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(54) **PYRAZOLYL GUANIDINE F<sub>1</sub>F<sub>0</sub>-ATPASE  
INHIBITORS AND THERAPEUTIC USES  
THEREOF**

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See application file for complete search history.

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(57) **ABSTRACT**

The invention provides pyrazolyl guanidine compounds that inhibit F<sub>1</sub>F<sub>0</sub>-ATPase, and methods of using pyrazolyl guanidine compounds as therapeutic agents to treat medical disorders, such as an immune disorder, inflammatory condition, or cancer.

**32 Claims, No Drawings**

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**PYRAZOLYL GUANIDINE F<sub>1</sub>F<sub>0</sub>-ATPASE  
INHIBITORS AND THERAPEUTIC USES  
THEREOF**

**CROSS REFERENCE TO RELATED  
APPLICATIONS**

This application is the national stage of International (PCT) Patent Application Serial No. PCT/US2011/063950, filed Dec. 8, 2011, which claims the benefit of and priority to U.S. Provisional Patent Application Ser. No. 61/420,950, filed Dec. 8, 2010, the contents of each application are hereby incorporated by reference.

**FIELD OF THE INVENTION**

The invention provides inhibitors of F<sub>1</sub>F<sub>0</sub>-ATPases (e.g., mitochondrial F<sub>1</sub>F<sub>0</sub>-ATPases) and their therapeutic use. In particular, the invention provides pyrazolyl guanidine compounds that inhibit F<sub>1</sub>F<sub>0</sub>-ATPase, and methods of using pyrazolyl guanidine compounds as therapeutic agents to treat a number of medical conditions.

**BACKGROUND**

Multicellular organisms exert precise control over cell number. A balance between cell proliferation and cell death achieves this homeostasis. Cell death occurs in nearly every type of vertebrate cell via necrosis or through a suicidal form of cell death, known as apoptosis. Apoptosis is triggered by a variety of extracellular and intracellular signals that engage a common, genetically programmed death mechanism.

Multicellular organisms use apoptosis to instruct damaged or unnecessary cells to destroy themselves for the good of the organism. Control of the apoptotic process therefore is very important to normal development, for example, fetal development of fingers and toes requires the controlled removal, by apoptosis, of excess interconnecting tissues, as does the formation of neural synapses within the brain. Similarly, controlled apoptosis is responsible for the sloughing off of the inner lining of the uterus (the endometrium) at the start of menstruation. While apoptosis plays an important role in tissue sculpting and normal cellular maintenance, it is also a component of the primary defense against cells and invaders (e.g., viruses) which threaten the well being of the organism.

Not surprisingly many diseases are associated with dysregulation of apoptotic cell death. Experimental models have established a cause-effect relationship between aberrant apoptotic regulation and the pathogenicity of various neoplastic, autoimmune and viral diseases. For instance, in the cell-mediated immune response, effector cells (e.g., cytotoxic T lymphocytes "CTLs") destroy virus-infected cells by inducing the infected cells to undergo apoptosis. The organism subsequently relies on the apoptotic process to destroy the effector cells when they are no longer needed. Autoimmunity is normally prevented by the CTLs inducing apoptosis in each other and even in themselves. Defects in this process are associated with a variety of immune diseases such as lupus erythematosus and rheumatoid arthritis.

Multicellular organisms also use apoptosis to instruct cells with damaged nucleic acids (e.g., DNA) to destroy themselves prior to becoming cancerous. Some cancer-causing viruses overcome this safeguard by reprogramming infected (transformed) cells to abort the normal apoptotic process. For example, several human papilloma viruses (HPVs) have been implicated in causing cervical cancer by suppressing the apoptotic removal of transformed cells by producing a protein

(E6) which inactivates the p53 apoptosis promoter. Similarly, the Epstein-Barr virus (EBV), the causative agent of mononucleosis and Burkitt's lymphoma, reprograms infected cells to produce proteins that prevent normal apoptotic removal of the aberrant cells thus allowing the cancerous cells to proliferate and to spread throughout the organism.

Still other viruses destructively manipulate a cell's apoptotic machinery without directly resulting in the development of a cancer. For example, destruction of the immune system in individuals infected with the human immunodeficiency virus (HIV) is thought to progress through infected CD4<sup>+</sup> T cells (about 1 in 100,000) instructing uninfected sister cells to undergo apoptosis.

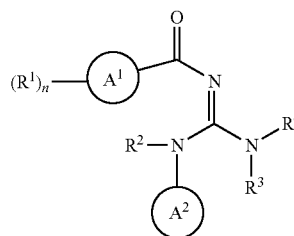
Some cancers that arise by non-viral means have also developed mechanisms to escape destruction by apoptosis. Melanoma cells, for instance, avoid apoptosis by inhibiting the expression of the gene encoding Apaf-1. Other cancer cells, especially lung and colon cancer cells, secrete high levels of soluble decoy molecules that inhibit the initiation of CTL mediated clearance of aberrant cells. Faulty regulation of the apoptotic machinery has also been implicated in various degenerative conditions and vascular diseases.

Controlled regulation of the apoptotic process and its cellular machinery is important to the survival of multicellular organisms. Typically, the biochemical changes that occur in a cell instructed to undergo apoptosis occur in an orderly procession. However, as shown above, flawed regulation of apoptosis can cause serious deleterious effects in the organism.

The need exists for improved compositions and methods for regulating the apoptotic processes in subjects afflicted with diseases and conditions characterized by faulty regulation of these processes (e.g., viral infections, hyperproliferative autoimmune disorders, chronic inflammatory conditions, and cancers). The present invention addresses this need and provides other related advantages.

**SUMMARY**

The invention provides pyrazolyl guanidine compounds that inhibit F<sub>1</sub>F<sub>0</sub>-ATPase (e.g., mitochondrial F<sub>1</sub>F<sub>0</sub>-ATPase), pharmaceutical compositions comprising pyrazolyl guanidine compounds, and methods of using such compounds and pharmaceutical compositions to treat a number of medical conditions. Accordingly, one aspect of the invention provides a family of compounds represented by Formula I:

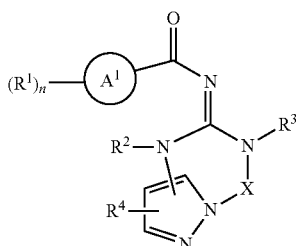


(I)

including all stereoisomers, geometric isomers, and tautomers; or a pharmaceutically acceptable salt or solvate of any of the foregoing; wherein the variables are as defined in the detailed description.

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Another aspect of the invention provides a family of compounds represented by Formula II:



including all stereoisomers, geometric isomers, and tautomers; or a pharmaceutically acceptable salt or solvate of any of the foregoing; wherein the variables are as defined in the detailed description.

The foregoing compounds can be present in a pharmaceutical composition comprising a compound described herein and a pharmaceutically acceptable carrier.

Another aspect of the invention provides a method of treating a subject suffering from a medical disorder. The method comprises administering to the subject a therapeutically effective amount of one or more pyrazolyl guanidine compounds described herein, e.g., a compound of Formula I or II, in order to ameliorate a symptom of the disorder. A large number of disorders can be treated using the pyrazolyl guanidine compounds described herein. For example, the compounds described herein can be used to treat an immune disorder or inflammatory disorder, such as rheumatoid arthritis, psoriasis, chronic graft-versus-host disease, acute graft-versus-host disease, Crohn's disease, inflammatory bowel disease, multiple sclerosis, systemic lupus erythematosus, Celiac Sprue, idiopathic thrombocytopenic thrombotic purpura, myasthenia gravis, Sjogren's syndrome, scleroderma, ulcerative colitis, asthma, epidermal hyperplasia, and other medical disorders described herein. The compounds described herein can also be used to treat a cardiovascular disease, myeloma, lymphoma, cancer, or bacterial infection.

Another aspect of the invention provides a method of inhibiting an  $F_1F_0$ -ATPase, for example, a mitochondrial  $F_1F_0$ -ATPase. The method comprises exposing the  $F_1F_0$ -ATPase to a compound described herein, such as a compound of Formula I or II, to inhibit said  $F_1F_0$ -ATPase.

#### DETAILED DESCRIPTION OF THE INVENTION

The invention provides pyrazolyl guanidine compounds that inhibit  $F_1F_0$ -ATPase (e.g., mitochondrial  $F_1F_0$ -ATPase), pharmaceutical compositions comprising the pyrazolyl guanidine compounds, and methods of using the pyrazolyl guanidine compounds and pharmaceutical compositions in therapy.

Exemplary compositions and methods of the present invention are described in more detail in the following sections: I. Modulators of  $F_1F_0$ -ATPase Activity; II. Pyrazolyl Guanidine Compounds; III. Therapeutic Applications of Pyrazolyl Guanidine Compounds, and IV. Pharmaceutical Compositions, Formulations, and Exemplary Administration Routes and Dosing Considerations. Aspects of the invention described in one particular section are not to be limited to any particular section.

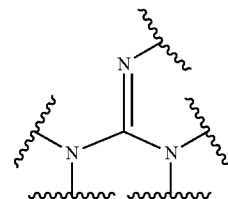
The practice of the present invention employs, unless otherwise indicated, conventional techniques of organic chem-

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istry, pharmacology, molecular biology (including recombinant techniques), cell biology, biochemistry, and immunology, which are within the skill of the art. Such techniques are explained fully in the literature, such as "Comprehensive Organic Synthesis" (B. M. Trost & I. Fleming, eds., 1991-1992); "Molecular cloning: a laboratory manual" Second Edition (Sambrook et al., 1989); "Oligonucleotide synthesis" (M. J. Gait, ed., 1984); "Animal cell culture" (R. I. Freshney, ed., 1987); the series "Methods in enzymology" (Academic Press, Inc.); "Handbook of experimental immunology" (D. M. Weir & C. C. Blackwell, eds.); "Gene transfer vectors for mammalian cells" (J. M. Miller & M. P. Calos, eds., 1987); "Current protocols in molecular biology" (F. M. Ausubel et al., eds., 1987, and periodic updates); "PCR: the polymerase chain reaction" (Mullis et al., eds., 1994); and "Current protocols in immunology" (J. E. Coligan et al., eds., 1991), each of which is herein incorporated by reference in its entirety.

To facilitate an understanding of the present invention, a number of terms and phrases are defined below.

As used herein, the term "guanidine" refers to a compound having the following core structure:



including pharmaceutically acceptable salt forms.

The term "alkyl" refers to a saturated straight or branched hydrocarbon, such as a straight or branched group of 1-12, 1-10, or 1-6 carbon atoms, referred to herein as  $C_1$ - $C_{12}$ alkyl,  $C_1$ - $C_{10}$ alkyl, and  $C_1$ - $C_6$ alkyl, respectively. Exemplary alkyl groups include, but are not limited to, methyl, ethyl, propyl, isopropyl, 2-methyl-1-propyl, 2-methyl-2-propyl, 2-methyl-1-butyl, 3-methyl-1-butyl, 2-methyl-3-butyl, 2,2-dimethyl-1-propyl, 2-methyl-1-pentyl, 3-methyl-1-pentyl, 4-methyl-1-pentyl, 2-methyl-2-pentyl, 3-methyl-2-pentyl, 4-methyl-2-pentyl, 2,2-dimethyl-1-butyl, 3,3-dimethyl-1-butyl, 2-ethyl-1-butyl, butyl, isobutyl, t-butyl, pentyl, isopentyl, neopentyl, hexyl, heptyl, octyl, etc.

The term "alkylene" refers to a diradical of an alkyl group. Exemplary alkylene groups include  $-CH_2-$  and  $-CH_2CH_2-$ .

The term "haloalkyl" refers to an alkyl group that is substituted with at least one halogen. For example,  $-CH_2F$ ,  $-CHF_2$ ,  $-CF_3$ ,  $-CH_2CF_3$ ,  $-CF_2CF_3$ , and the like.

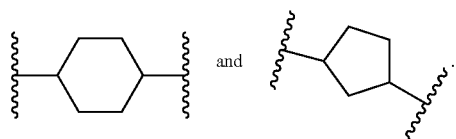
The term "hydroxyalkyl" refers to an alkyl group that is substituted with at least one hydroxyl group. In certain embodiments, the hydroxyalkyl group is an alkyl group that is substituted with one hydroxyl group.

The term "cycloalkyl" refers to a monovalent saturated cyclic, bicyclic, or bridged cyclic (e.g., adamantyl)hydrocarbon group of 3-12, 3-8, 4-8, or 4-6 carbons, referred to herein, e.g., as " $C_{4-8}$ cycloalkyl," derived from a cycloalkane. Exemplary cycloalkyl groups include cyclohexyl, cyclopentyl, cyclobutyl, and cyclopropyl.

The term "cycloalkylene" refers to a divalent (i.e., diradical) saturated cyclic, bicyclic, or bridged cyclic (e.g., adamantyl)hydrocarbon group of 3-12, 3-8, 4-8, or 4-6 carbons, referred to herein, e.g., as " $C_{4-8}$ cycloalkylene," derived from a cycloalkane. Unless specified otherwise, the cycloalkylene may be substituted at one or more ring positions with, for example, halogen, azide, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, alkoxy, amino, nitro, sulphydryl,

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imino, amido, carboxylic acid,  $\text{—C(O)alkyl}$ ,  $\text{—CO}_2\text{alkyl}$ , carbonyl, carboxyl, alkylthio, sulfonyl, sulfonamido, sulfonamide, ketone, aldehyde, ester, heterocyclyl, aryl, heteroaryl,  $\text{—CF}_3$ ,  $\text{—CN}$ , or the like. In certain embodiments, the cycloalkylene group is substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, hydroxyl, alkoxy, and amino. In certain other embodiments, the cycloalkylene group is not substituted, i.e., it is unsubstituted. Exemplary cycloalkylene groups include



The term “aralkyl” refers to an alkyl group substituted with an aryl group.

The term “heteroaralkyl” refers to an alkyl group substituted with a heteroaryl group.

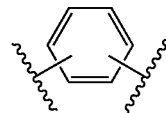
The term “alkenyl” refers to an unsaturated straight or branched hydrocarbon having at least one carbon-carbon double bond, such as a straight or branched group of 2-12, 2-10, or 2-6 carbon atoms, referred to herein as  $\text{C}_2\text{—C}_{12}\text{alkenyl}$ ,  $\text{C}_2\text{—C}_{10}\text{alkenyl}$ , and  $\text{C}_2\text{—C}_6\text{alkenyl}$ , respectively. Exemplary alkenyl groups include, but are not limited to, vinyl, allyl, butenyl, pentenyl, hexenyl, butadienyl, penta- dienyl, hexadienyl, 2-ethylhexenyl, 2-propyl-2-butenyl, 4-(2-methyl-3-butene)-pentenyl, etc.

The term “alkynyl” as used herein refers to an unsaturated straight or branched hydrocarbon having at least one carbon-carbon triple bond, such as a straight or branched group of 2-12, 2-8, or 2-6 carbon atoms, referred to herein as  $\text{C}_2\text{—C}_{12}\text{alkynyl}$ ,  $\text{C}_2\text{—C}_8\text{alkynyl}$ , and  $\text{C}_2\text{—C}_6\text{alkynyl}$ , respectively. Exemplary alkynyl groups include, but are not limited to, ethynyl, propynyl, butynyl, pentynyl, hexynyl, methylpropynyl, 4-methyl-1-butylnyl, 4-propyl-2-pentynyl, and 4-butylnyl-2-hexynyl, etc.

The term “aryl” is art-recognized and refers to a carbocyclic aromatic group. Representative aryl groups include phenyl, naphthyl, anthracenyl, and the like. Unless specified otherwise, the aromatic ring may be substituted at one or more ring positions with, for example, halogen, azide, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, alkoxy, amino, nitro, sulfhydryl, imino, amido, carboxylic acid,  $\text{—C(O)alkyl}$ ,  $\text{—CO}_2\text{alkyl}$ , carbonyl, carboxyl, alkylthio, sulfonyl, sulfonamido, sulfonamide, ketone, aldehyde, ester, heterocyclyl, heteroaryl,  $\text{—CF}_3$ ,  $\text{—CN}$ , or the like. The term “aryl” also includes polycyclic ring systems having two or more carbocyclic rings in which two or more carbons are common to two adjoining rings (the rings are “fused rings”) wherein at least one of the rings is aromatic, and the other ring(s) may be, for example, cycloalkyl, cycloalkenyl, cycloalkynyl, and/or aryl. The term “haloaryl” refers to an aryl group that is substituted with at least one halogen. In certain embodiments, the aromatic group is not substituted, i.e., it is unsubstituted.

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The term “phenylene” refers to a multivalent radical (e.g., a divalent or trivalent radical) of benzene. To illustrate, a divalent valent radical of benzene is illustrated by the formula

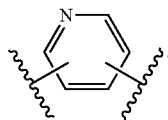


The terms “heterocyclyl” or “heterocyclic group” are art-recognized and refer to saturated, partially unsaturated, or aromatic 3- to 10-membered ring structures, alternatively 3- to 7-membered rings, whose ring structures include one to four heteroatoms, such as nitrogen, oxygen, and sulfur. Heterocycles may also be mono-, bi-, or other multi-cyclic ring systems. A heterocycle may be fused to one or more aryl, partially unsaturated, or saturated rings. Heterocyclyl groups include, for example, biotinyl, chromenyl, dihydrofuryl, dihydroindolyl, dihydropyranyl, dihydrothienyl, dithiazolyl, homopiperidinyl, imidazolidinyl, isoquinolyl, isothiazolidinyl, isoxazolidinyl, morpholinyl, oxolanyl, oxazolidinyl, phenoxanthenyl, piperazinyl, piperidinyl, pyranyl, pyrazolidinyl, pyrazolinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolidin-2-onyl, pyrrolinyl, tetrahydrofuryl, tetrahydroisoquinolyl, tetrahydropyranyl, tetrahydroquinolyl, thiazolidinyl, thiolanyl, thiomorpholinyl, thiopyranyl, xanthenyl, lactones, lactams such as azetidinones and pyrrolidinones, sultams, sultones, and the like. Unless specified otherwise, the heterocyclic ring is optionally substituted at one or more positions with substituents such as alkanoyl, alkoxy, alkyl, alkenyl, alkynyl, amido, amidino, amino, aryl, arylalkyl, azido, carbamate, carbonate, carboxy, cyano, cycloalkyl, ester, ether, formyl, halogen, haloalkyl, heteroaryl, heterocyclyl, hydroxyl, imino, ketone, nitro, phosphate, phosphonato, phosphinato, sulfate, sulfide, sulfonamido, sulfonyl and thiocarbonyl. In certain embodiments, the heterocyclyl group is not substituted, i.e., it is unsubstituted.

The term “heteroaryl” is art-recognized and refers to aromatic groups that include at least one ring heteroatom. In certain instances, a heteroaryl group contains 1, 2, 3, or 4 ring heteroatoms. Representative examples of heteroaryl groups includes pyrrolyl, furanyl, thiophenyl, imidazolyl, oxazolyl, thiazolyl, triazolyl, pyrazolyl, pyridinyl, pyrazinyl, pyridazinyl and pyrimidinyl, and the like. Unless specified otherwise, the heteroaryl ring may be substituted at one or more ring positions with, for example, halogen, azide, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, alkoxy, amino, nitro, sulfhydryl, imino, amido, carboxylic acid,  $\text{—C(O)alkyl}$ ,  $\text{—CO}_2\text{alkyl}$ , carbonyl, carboxyl, alkylthio, sulfonyl, sulfonamido, sulfonamide, ketone, aldehyde, ester, heterocyclyl, aryl,  $\text{—CF}_3$ ,  $\text{—CN}$ , or the like. The term “heteroaryl” also includes polycyclic ring systems having two or more rings in which two or more carbons are common to two adjoining rings (the rings are “fused rings”) wherein at least one of the rings is heteroaromatic, and the other ring(s) may be, for example, cycloalkyl, cycloalkenyl, cycloalkynyl, and/or aryl.

The term “heteroarylene” refers to a multi-valent (e.g., di-valent or trivalent) aromatic group that comprises at least one ring heteroatom. An exemplary “heteroarylene” is pyridinylene, which is a multi-valent radical of pyridine. For example, a divalent radical of pyridine is illustrated by the formula

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The terms ortho, meta and para are art-recognized and refer to 1,2-, 1,3- and 1,4-disubstituted benzenes, respectively. For example, the names 1,2-dimethylbenzene and ortho-dimethylbenzene are synonymous.

The terms "amine" and "amino" are art-recognized and refer to both unsubstituted and substituted amines, e.g., a moiety that may be represented by the general formula:



wherein  $R^{50}$  and  $R^{51}$  each independently represent hydrogen, alkyl, alkenyl, or  $-(CH_2)_m-R^{61}$ ; or  $R^{50}$  and  $R^{51}$ , taken together with the N atom to which they are attached complete a heterocycle having from 4 to 8 atoms in the ring structure; wherein  $R^{61}$  is aryl, cycloalkyl, cycloalkenyl, a heterocycle or a polycycle; and m is zero or an integer in the range of 1 to 8. In certain embodiments,  $R^{50}$  and  $R^{51}$  each independently represent hydrogen or alkyl.

The terms "alkoxyl" or "alkoxy" are art-recognized and refer to an alkyl group, as defined above, having an oxygen radical attached thereto. Representative alkoxyl groups include methoxy, ethoxy, propyloxy, tert-butoxy and the like. An "ether" is two hydrocarbons covalently linked by an oxygen. Accordingly, the substituent of an alkyl that renders that alkyl an ether is or resembles an alkoxyl, such as may be represented by one of  $-O$ -alkyl,  $-O$ -alkenyl,  $-O$ -alkynyl,  $-O-(CH_2)_m-R^{61}$ , where m and  $R^{61}$  are described above.

The term "amide" or "amido" as used herein refers to a radical of the form  $-R_aC(O)N(R_b)-$ ,  $-R_aC(O)N(R_b)R_c-$ ,  $-C(O)NR_bR_c-$ , or  $-C(O)NH_2$ , wherein  $R_a$ ,  $R_b$  and  $R_c$  are each independently selected from alkoxy, alkyl, alkenyl, alkynyl, amide, amino, aryl, arylalkyl, carbamate, cycloalkyl, ester, ether, formyl, halogen, haloalkyl, heteroaryl, heterocyclyl, hydrogen, hydroxyl, ketone, and nitro. The amide can be attached to another group through the carbon, the nitrogen,  $R_b$ ,  $R_c$ , or  $R_a$ . The amide also may be cyclic, for example  $R_b$  and  $R_c$ ,  $R_a$  and  $R_b$ , or  $R_a$  and  $R_c$ , may be joined to form a 3- to 12-membered ring, such as a 3- to 10-membered ring or a 5- to 6-membered ring. The term "carboxamido" refers to the structure  $-C(O)NR_bR_c$ .

The term "sulfonamide" or "sulfonamido" as used herein refers to a radical having the structure  $-N(R_s)-S(O)_2-R_t-$  or  $-S(O)_2-N(R_s)R_t$ , where  $R_s$  and  $R_t$  can be, for example, hydrogen, alkyl, aryl, cycloalkyl, and heterocyclyl. Exemplary sulfonamides include alkylsulfonamides (e.g., where  $R_s$  is alkyl), arylsulfonamides (e.g., where  $R_s$  is aryl), cycloalkyl sulfonamides (e.g., where  $R_s$  is cycloalkyl), and heterocyclyl sulfonamides (e.g., where  $R_s$  is heterocyclyl), etc.

The term "sulfonyl" as used herein refers to a radical having the structure  $R_uSO_2-$ , where  $R_u$  can be alkyl, aryl, cycloalkyl, and heterocyclyl, e.g., alkylsulfonyl. The term "alkylsulfonyl" as used herein refers to an alkyl group attached to a sulfonyl group.

The symbol " $\sim$ " indicates a point of attachment.

The compounds of the disclosure may contain one or more chiral centers and/or double bonds and, therefore, exist as

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stereoisomers, such as geometric isomers, enantiomers or diastereomers. The term "stereoisomers" when used herein consist of all geometric isomers, enantiomers or diastereomers. These compounds may be designated by the symbols "R" or "S," depending on the configuration of substituents around the stereogenic carbon atom. Stereoisomers include enantiomers and diastereomers. Mixtures of enantiomers or diastereomers may be designated " $(\pm)$ " in nomenclature, but the skilled artisan will recognize that a structure may denote a chiral center implicitly. Unless indicated otherwise, generic chemical structures and graphical representations of specific compounds encompass all stereoisomers.

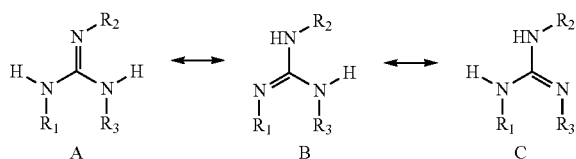
Individual stereoisomers of compounds of the present invention can be prepared synthetically from commercially available starting materials that contain asymmetric or stereogenic centers, or by preparation of racemic mixtures followed by resolution methods well known to those of ordinary skill in the art. These methods of resolution are exemplified by (1) attachment of a mixture of enantiomers to a chiral auxiliary, separation of the resulting mixture of diastereomers by recrystallization or chromatography and liberation of the optically pure product from the auxiliary, (2) salt formation employing an optically active resolving agent, or (3) direct separation of the mixture of optical enantiomers on chiral chromatographic columns. Stereoisomeric mixtures can also be resolved into their component stereoisomers by well known methods, such as chiral-phase gas chromatography, chiral-phase high performance liquid chromatography, crystallizing the compound as a chiral salt complex, or crystallizing the compound in a chiral solvent. Stereoisomers can also be obtained from stereomerically-pure intermediates, reagents, and catalysts by well known asymmetric synthetic methods.

Geometric isomers can also exist in the compounds of the present invention. The symbol  $=$  denotes a bond that may be a single, double or triple bond as described herein. The present invention encompasses the various geometric isomers and mixtures thereof resulting from the arrangement of substituents around a carbon-carbon double bond or arrangement of substituents around a carbocyclic ring. Substituents around a carbon-carbon double bond are designated as being in the "Z" or "E" configuration wherein the terms "Z" and "E" are used in accordance with IUPAC standards. Unless otherwise specified, structures depicting double bonds encompass both the "E" and "Z" isomers.

Substituents around a carbon-carbon double bond alternatively can be referred to as "cis" or "trans," where "cis" represents substituents on the same side of the double bond and "trans" represents substituents on opposite sides of the double bond. The arrangement of substituents around a carbocyclic ring are designated as "cis" or "trans." The term "cis" represents substituents on the same side of the plane of the ring and the term "trans" represents substituents on opposite sides of the plane of the ring. Mixtures of compounds wherein the substituents are disposed on both the same and opposite sides of plane of the ring are designated "cis/trans."

Certain compounds described herein may exist as a single tautomer or as a mixture of tautomers. For example, certain guanidine compounds having a hydrogen atom attached to at least one of the guanidine nitrogen atoms can exist as a single tautomer or a mixture of tautomers. To illustrate, depending upon the substituents attached at the  $R^1$ ,  $R^2$  and  $R^3$  positions, the guanidine compound may exist as a single tautomer represented by A, B, or C, or as mixture of two or more of A, B, and C.

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The compounds disclosed herein can exist in solvated as well as unsolvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like, and it is intended that the invention embrace both solvated and unsolvated forms.

The invention also embraces isotopically labeled compounds of the invention which are identical to those recited herein, except that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, fluorine and chlorine, such as <sup>2</sup>H, <sup>3</sup>H, <sup>13</sup>C, <sup>14</sup>C, <sup>15</sup>N, <sup>18</sup>O, <sup>17</sup>O, <sup>31</sup>P, <sup>32</sup>P, <sup>35</sup>S, <sup>18</sup>F, and <sup>36</sup>Cl, respectively.

Certain isotopically-labeled disclosed compounds (e.g., those labeled with <sup>3</sup>H and <sup>14</sup>C) are useful in compound and/or substrate tissue distribution assays. Tritiated (i.e., <sup>3</sup>H) and carbon-14 (i.e., <sup>14</sup>C) isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium (i.e., <sup>2</sup>H) may afford certain therapeutic advantages resulting from greater metabolic stability (e.g., increased in vivo half-life or reduced dosage requirements) and hence may be preferred in some circumstances. Isotopically labeled compounds of the invention can generally be prepared by following procedures analogous to those disclosed in the e.g., Examples herein by substituting an isotopically labeled reagent for a non-isotopically labeled reagent.

The term "IC<sub>50</sub>" is art-recognized and refers to the concentration of a compound that is required for 50% inhibition of its target.

The term "EC<sub>50</sub>" is art-recognized and refers to the concentration of a compound at which 50% of its maximal effect is observed.

The terms "subject" and "patient" refer to organisms to be treated by the methods of the present invention. Such organisms preferably include, but are not limited to, mammals (e.g., murines, simians, equines, bovines, porcines, canines, felines, and the like), and most preferably includes humans. In the context of the invention, the terms "subject" and "patient" generally refer to an individual who will receive or who has received treatment (e.g., administration of a compound of the present invention and optionally one or more other agents) for a condition characterized by the dysregulation of apoptotic processes.

As used herein, the term "effective amount" refers to the amount of a compound sufficient to effect beneficial or desired results. An effective amount can be administered in one or more administrations, applications or dosages and is not intended to be limited to a particular formulation or administration route. As used herein, the term "treating" includes any effect, e.g., lessening, reducing, modulating, ameliorating or eliminating, that results in the improvement of the condition, disease, disorder, and the like, or ameliorating a symptom thereof.

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The phrase "pathologically proliferating or growing cells" refers to a localized population of proliferating cells in an animal that is not governed by the usual limitations of normal growth.

As used herein, the term "un-activated target cell" refers to a cell that is either in the G<sub>0</sub> phase or one to which a stimulus has not been applied.

As used herein, the term "activated target lymphoid cell" refers to a lymphoid cell that has been primed with an appropriate stimulus to cause a signal transduction cascade, or alternatively, a lymphoid cell that is not in G<sub>0</sub> phase. Activated lymphoid cells may proliferate, undergo activation induced cell death, or produce one or more cytotoxins, cytokines, or other related membrane-associated proteins characteristic of the cell type (e.g., CD8<sup>+</sup> or CD4<sup>+</sup>). They are also capable of recognizing and binding any target cell that displays a particular antigen on its surface, and subsequently releasing its effector molecules.

As used herein, the term "activated cancer cell" refers to a cancer cell that has been primed with an appropriate stimulus to cause signal transduction. An activated cancer cell may or may not be in the G<sub>0</sub> phase.

An activating agent is a stimulus that upon interaction with a target cell results in a signal transduction cascade. Examples of activating stimuli include, but are not limited to, small molecules, radiant energy, and molecules that bind to cell activation cell surface receptors. Responses induced by activation stimuli can be characterized by changes in, among others, intracellular Ca<sup>2+</sup>, superoxide, or hydroxyl radical levels; the activity of enzymes like kinases or phosphatases; or the energy state of the cell. For cancer cells, activating agents also include transforming oncogenes.

As used herein, the term "dysregulation of the process of cell death" refers to any aberration in the ability (e.g., predisposition) of a cell to undergo cell death via either necrosis or apoptosis. Dysregulation of cell death is associated with or induced by a variety of conditions, including for example, immune disorders (e.g., systemic lupus erythematosus, autoimmune disorders, rheumatoid arthritis, graft-versus-host disease, myasthenia gravis, Sjögren's syndrome, etc.), chronic inflammatory conditions (e.g., psoriasis, asthma and Crohn's disease), hyperproliferative disorders (e.g., tumors, B cell lymphomas, T cell lymphomas, etc.), viral infections (e.g., herpes, papilloma, HIV), and other conditions such as osteoarthritis and atherosclerosis.

It should be noted that when the dysregulation is induced by or associated with a viral infection, the viral infection may or may not be detectable at the time dysregulation occurs or is observed. That is, viral-induced dysregulation can occur even after the disappearance of symptoms of viral infection.

A "hyperproliferative disorder," as used herein refers to any condition in which a localized population of proliferating cells in an animal is not governed by the usual limitations of normal growth. Examples of hyperproliferative disorders include tumors, neoplasms, lymphomas and the like. A neoplasm is said to be benign if it does not undergo invasion or metastasis and malignant if it does either of these. A metastatic cell or tissue means that the cell can invade and destroy neighboring body structures. Hyperplasia is a form of cell proliferation involving an increase in cell number in a tissue or organ, without significant alteration in structure or function. Metaplasia is a form of controlled cell growth in which one type of fully differentiated cell substitutes for another type of differentiated cell. Metaplasia can occur in epithelial or connective tissue cells. A typical metaplasia involves a somewhat disorderly metaplastic epithelium.

The pathological growth of activated lymphoid cells often results in an immune disorder or a chronic inflammatory condition. As used herein, the term "immune disorder" refers to any condition in which an organism produces antibodies or immune cells which recognize the organism's own molecules, cells or tissues. Non-limiting examples of immune disorders include autoimmune disorders, immune hemolytic anemia, immune hepatitis, Berger's disease or IgA nephropathy, Celiac Sprue, chronic fatigue syndrome, Crohn's disease, dermatomyositis, fibromyalgia, graft-versus-host disease, Grave's disease, Hashimoto's thyroiditis, idiopathic thrombocytopenia purpura, lichen planus, multiple sclerosis, myasthenia gravis, psoriasis, rheumatic fever, rheumatic arthritis, scleroderma, Sjorgren syndrome, systemic lupus erythematosus, type 1 diabetes, ulcerative colitis, vitiligo, tuberculosis, and the like.

As used herein, the term "chronic inflammatory condition" refers to a condition wherein the organism's immune cells are activated. Such a condition is characterized by a persistent inflammatory response with pathologic sequelae. This state is characterized by infiltration of mononuclear cells, proliferation of fibroblasts and small blood vessels, increased connective tissue, and tissue destruction. Examples of chronic inflammatory diseases include, but are not limited to, Crohn's disease, psoriasis, chronic obstructive pulmonary disease, inflammatory bowel disease, multiple sclerosis, and asthma. Immune diseases such as rheumatoid arthritis and systemic lupus erythematosus can also result in a chronic inflammatory state.

As used herein, the term "co-administration" refers to the administration of at least two agent(s) (e.g., a compound of the present invention) or therapies to a subject. In some embodiments, the co-administration of two or more agents/therapies is concurrent. In other embodiments, a first agent/therapy is administered prior to a second agent/therapy. Those of skill in the art understand that the formulations and/or routes of administration of the various agents/therapies used may vary. The appropriate dosage for co-administration can be readily determined by one skilled in the art. In some embodiments, when agents/therapies are co-administered, the respective agents/therapies are administered at lower dosages than appropriate for their administration alone. Thus, co-administration is especially desirable in embodiments where the co-administration of the agents/therapies lowers the requisite dosage of a known potentially harmful (e.g., toxic) agent(s).

As used herein, the term "pharmaceutical composition" refers to the combination of an active agent with a carrier, inert or active, making the composition especially suitable for diagnostic or therapeutic use in vivo or ex vivo.

As used herein, the term "pharmaceutically acceptable carrier" refers to any of the standard pharmaceutical carriers, such as a phosphate buffered saline solution, water, emulsions (e.g., such as an oil/water or water/oil emulsions), and various types of wetting agents. The compositions also can include stabilizers and preservatives. For examples of carriers, stabilizers and adjuvants. (See e.g., Martin, Remington's Pharmaceutical Sciences, 15th Ed., Mack Publ. Co., Easton, Pa. [1975]).

As used herein, the term "pharmaceutically acceptable salt" refers to any pharmaceutically acceptable salt (e.g., acid or base) of a compound of the present invention which, upon administration to a subject, is capable of providing a compound of this invention or an active metabolite or residue thereof. As is known to those of skill in the art, "salts" of the compounds of the present invention may be derived from inorganic or organic acids and bases. Examples of acids

include, but are not limited to, hydrochloric, hydrobromic, sulfuric, nitric, perchloric, fumaric, maleic, phosphoric, glycolic, lactic, salicylic, succinic, toluene-p-sulfonic, tartaric, acetic, citric, methanesulfonic, ethanesulfonic, formic, benzoic, malonic, naphthalene-2-sulfonic, benzenesulfonic acid, and the like. Other acids, such as oxalic, while not in themselves pharmaceutically acceptable, may be employed in the preparation of salts useful as intermediates in obtaining the compounds of the invention and their pharmaceutically acceptable acid addition salts.

Examples of bases include, but are not limited to, alkali metals (e.g., sodium) hydroxides, alkaline earth metals (e.g., magnesium), hydroxides, ammonia, and compounds of formula  $NW_4^+$ , wherein W is  $C_{1-4}$  alkyl, and the like.

Examples of salts include, but are not limited to: acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, flucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, oxalate, palmoate, pectinate, persulfate, phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, tosylate, undecanoate, and the like. Other examples of salts include anions of the compounds of the present invention compounded with a suitable cation such as  $Na^+$ ,  $NH_4^+$ , and  $NW_4^+$  (wherein W is a  $C_{1-4}$  alkyl group), and the like.

For therapeutic use, salts of the compounds of the present invention are contemplated as being pharmaceutically acceptable. However, salts of acids and bases that are non-pharmaceutically acceptable may also find use, for example, in the preparation or purification of a pharmaceutically acceptable compound.

As used herein, the term "modulate" refers to the activity of a compound (e.g., a compound of the present invention) to affect (e.g., to promote or retard) an aspect of cellular function, including, but not limited to, cell growth, proliferation, apoptosis, and the like.

Throughout the description, where compositions are described as having, including, or comprising specific components, or where processes and methods are described as having, including, or comprising specific steps, it is contemplated that, additionally, there are compositions of the present invention that consist essentially of, or consist of, the recited components, and that there are processes and methods according to the present invention that consist essentially of, or consist of, the recited processing steps.

As a general matter, compositions specifying a percentage are by weight unless otherwise specified. Further, if a variable is not accompanied by a definition, then the previous definition of the variable controls.

#### I. Modulators of $F_1F_0$ -ATPase Activity

In some embodiments, the present invention regulates  $F_1F_0$ -ATPase activity (e.g., mitochondrial  $F_1F_0$ -ATPase activity) through the exposure of cells to compounds of the present invention. In some embodiments, the compounds inhibit ATP synthesis and ATP hydrolysis. The effect of the compounds can be measured by detecting any number of cellular changes. For example, mitochondrial  $F_1F_0$ -ATPase activity and/or cell death may be assayed as described herein and in the art. In some embodiments, cell lines are maintained under appropriate cell culturing conditions (e.g., gas ( $CO_2$ ), temperature and media) for an appropriate period of time to attain exponential proliferation without density dependent constraints. Cell number and/or viability are measured using



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standard techniques, such as trypan blue exclusion/hemocytometry, or an Alamar Blue or MTT dye conversion assay. Alternatively, the cell may be analyzed for the expression of genes or gene products associated with aberrations in apoptosis or necrosis.

In some embodiments, exposing the compounds of the present invention to a cell induces apoptosis. In some embodiments, the present invention induces apoptosis or arrest of cell proliferation through interacting with the mitochondrial  $F_1F_0$ -ATPase. In some embodiments, the compounds of the present invention inhibit mitochondrial  $F_1F_0$ -ATPase activity through binding the OSCP. In some embodiments, the compounds of the present invention bind the junction between the OSCP and the  $F_1$  subunit of the mitochondrial  $F_1F_0$ -ATPase. In some embodiments, the compounds of the present invention bind the  $F_1$  subunit. In certain embodiments, screening assays of the present invention permit detection of binding partners of the OSCP,  $F_1$ , or OSCP/ $F_1$  junction.

In some embodiments, exposing a compound of the present invention to a cell induces apoptosis. In some embodiments, the present invention causes an initial increase in cellular ROS levels (e.g.,  $O_2^-$ ). In further embodiments, exposure of the compounds of the present invention to a cell causes an increase in cellular  $O_2^-$  levels. In still further embodiments, the increase in cellular  $O_2^-$  levels resulting from the compounds of the present invention is detectable with a redox-sensitive agent that reacts specifically with  $O_2^-$  (e.g., dihydroethidium (DHE)).

In some embodiments, the present invention causes a collapse of a cell's mitochondrial transmembrane potential ( $\Delta\Psi_m$ ). In some embodiments, a collapse of a cell's mitochondrial  $\Delta\Psi_m$  resulting from the present invention is detectable with a mitochondria-selective potentiometric probe (e.g., 3,3'-Diheptyloxycarbocyanine iodide, DiOC<sub>6</sub>). In further embodiments, a collapse of a cell's mitochondrial  $\Delta\Psi_m$  resulting from the present invention occurs after an initial increase in cellular  $O_2^-$  levels.

In some embodiments, the present invention enables caspase activation. In other embodiments, the present invention causes the release of cytochrome c from mitochondria. In further embodiments, the present invention alters cystolic cytochrome c levels. In still other embodiments, altered cystolic cytochrome c levels resulting from the present invention are detectable by immunoblotting cytosolic fractions. In some embodiments, diminished cystolic cytochrome c levels resulting from the present invention are detectable after a period of time (e.g., 10 hours). In further preferred embodiments, diminished cystolic cytochrome c levels resulting from the present invention are detectable after 5 hours.

In other embodiments, the present invention causes the opening of the mitochondrial permeability transition pore. In some embodiments, the cellular release of cytochrome c resulting from the present invention is consistent with a collapse of mitochondrial  $\Delta\Psi_m$ . In still further preferred embodiments, the present invention causes an increase in cellular  $O_2^-$  levels after a mitochondrial  $\Delta\Psi_m$  collapse and a release of cytochrome c. In further preferred embodiments, a rise in cellular  $O_2^-$  levels is caused by a mitochondrial  $\Delta\Psi_m$  collapse and release of cytochrome c resulting from the present invention.

In other embodiments, the present invention causes cellular caspase activation. In some embodiments, caspase activation resulting from the present invention is measurable with a pan-caspase sensitive fluorescent substrate (e.g., FAM-VAD-fmk). In still further embodiments, caspase activation resulting from the present invention tracks with a collapse of mitochondrial  $\Delta\Psi_m$ . In other embodiments, the present invention

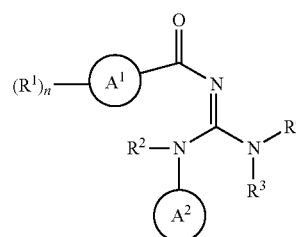
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causes an appearance of hypodiploid DNA. In some embodiments, an appearance of hypodiploid DNA resulting from the present invention is slightly delayed with respect to caspase activation.

In some embodiments, the molecular target for the present invention is found within mitochondria. In further embodiments, the molecular target of the present invention involves the mitochondrial ATPase. The primary sources of cellular ROS include redox enzymes and the mitochondrial respiratory chain (hereinafter MRC). In some embodiments, cytochrome c oxidase (complex IV of the MRC) inhibitors (e.g.,  $NaN_3$ ) preclude a present invention dependent increase in cellular ROS levels. In other preferred embodiments, the ubiquinol-cytochrome c reductase component of MRC complex III inhibitors (e.g., FK506) preclude a present invention dependent increase in ROS levels.

## II. Pyrazolyl Guanidine Compounds

One aspect of the invention provides a family of compounds represented by Formula I:

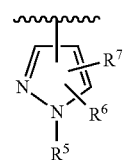


(I)

including all stereoisomers, geometric isomers, and tautomers; or a pharmaceutically acceptable salt or solvate of any of the foregoing; wherein:

$A^1$  is phenylene or a six-membered heteroarylene;

$A^2$  is



$R^1$  represents independently for each occurrence halogen, haloalkyl, alkyl, cycloalkyl, heterocycloalkyl, hydroxyl,  $C_1$ - $C_6$ alkoxy, cyano,  $-CO_2R^8$ ,  $-C(O)R^9$ ,  $-S(O)R^9$ ,  $-SO_2R^9$ ,  $-SO_2N(R^{10})(R^{11})C(O)N(R^{10})(R^{11})$ ,  $N(R^{10})(R^{11})$  or  $-N(R^8)C(O)(R^9)$ ;

$R^2$  is hydrogen or alkyl;

$R^3$  is aryl, aralkyl, cycloalkyl,  $-(C(R^8)_2)_m$ -cycloalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl,  $-(C(R^8)_2)_m$ -heterocycloalkyl, alkyl, haloalkyl, hydroxyalkyl,  $-(C(R^8)_2)_m$ -alkoxy,  $-(C(R^8)_2)_m$ -O- $-(C(R^8)_2)_m$ -alkoxy, or  $-(C(R^8)_2)_m$ -CN, wherein said aryl, aralkyl, cycloalkyl, heteroaryl, heteroaralkyl, and heterocycloalkyl are each optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, haloalkyl, hydroxyl, alkyl, cycloalkyl, hydroxyalkyl,  $C_1$ - $C_6$ alkoxy, cyano, and  $-C_1$ - $C_6$ alkylene- $CO_2R^8$ ;

$R^4$  is hydrogen, alkyl, or  $-C(O)R^9$ ; or  $R^3$  and  $R^4$  are taken together with the nitrogen atom to which they are attached to form a 3 to 7 membered heterocyclic ring optionally substi-

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tuted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, haloalkyl, hydroxyl, alkyl, cycloalkyl, and C<sub>1</sub>-C<sub>6</sub>alkoxy;

R<sup>5</sup> is hydrogen or alkyl;

R<sup>6</sup> is alkyl, cycloalkyl, haloalkyl, cyano, aryl, aralkyl, heteroaryl, heteroaralkyl, —CO<sub>2</sub>R<sup>8</sup>, or —C(O)N(R<sup>10</sup>)(R<sup>11</sup>) wherein said cycloalkyl, aryl, aralkyl, heteroaryl, and heteroaralkyl are each optionally substituted with 1 or 2 substituents independently selected from the group consisting of halogen, haloalkyl, hydroxyl, alkyl, hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>alkoxy, —O-aralkyl, and cyano;

R<sup>7</sup> is hydrogen, halogen, alkyl, or haloalkyl;

R<sup>8</sup> represents independently for each occurrence hydrogen, alkyl, or cycloalkyl; or two occurrences of R<sup>8</sup> attached to the same carbon atom are taken together with said carbon atom to form a saturated carbocyclic ring;

R<sup>9</sup> represents independently for each occurrence alkyl or cycloalkyl;

R<sup>10</sup> and R<sup>11</sup> each represent independently for each occurrence hydrogen, alkyl, or cycloalkyl; or R<sup>10</sup> and R<sup>11</sup> are taken together with the nitrogen atom to which they are attached to form a 3 to 7 membered heterocyclic ring optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, haloalkyl, hydroxyl, alkyl, cycloalkyl, and C<sub>1</sub>-C<sub>6</sub>alkoxy;

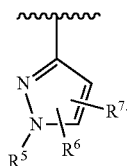
n is 0, 1, 2, or 3; and

m is 1, 2, 3, 4, or 5.

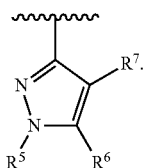
Definitions of the variables in Formula I above encompass multiple chemical groups. The application contemplates embodiments where, for example, i) the definition of a variable is a single chemical group selected from those chemical groups set forth above, ii) the definition is a collection of two or more of the chemical groups selected from those set forth above, and iii) the compound is defined by a combination of variables in which the variables are defined by (i) or (ii), e.g., such as where A<sup>1</sup> is phenylene, R<sup>1</sup> is halogen or haloalkyl, R<sup>2</sup> is hydrogen, and R<sup>4</sup> is hydrogen.

In certain embodiments, A<sup>1</sup> is phenylene. In certain embodiments, A<sup>1</sup> is a six-membered heteroarylene, such as pyridinyne or pyrimidinyne. In certain embodiments, A<sup>1</sup> is pyridinyne.

In certain embodiments, A<sup>2</sup> is



In certain embodiments, A<sup>2</sup> is



In certain embodiments, R<sup>1</sup> is halogen or haloalkyl. In certain embodiments, R<sup>1</sup> is chloro, fluoro, or trifluoromethyl.

In certain embodiments, R<sup>2</sup> is hydrogen. In certain embodiments, R<sup>2</sup> is alkyl, such as methyl or ethyl. In certain embodiments, R<sup>4</sup> is hydrogen. In certain embodiments, R<sup>4</sup> is alkyl,

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such as methyl or ethyl. In certain embodiments, R<sup>2</sup> and R<sup>4</sup> are hydrogen. In certain embodiments, R<sup>4</sup> is —C(O)R<sup>7</sup>. In certain embodiments, R<sup>2</sup> and R<sup>4</sup> are hydrogen.

In certain embodiments, R<sup>3</sup> is alkyl or cycloalkyl. In certain embodiments, R<sup>3</sup> is —(C(R<sup>8</sup>))<sub>m</sub>—alkoxy. In certain embodiments, R<sup>3</sup> is aryl or aralkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, haloalkyl, alkyl, and cycloalkyl. In certain embodiments, R<sup>3</sup> is phenyl optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, haloalkyl, alkyl, and cycloalkyl. In certain embodiments, R<sup>3</sup> is phenyl substituted with 1, 2, or 3 substituents independently selected from the group consisting of chloro, fluoro, trifluoromethyl, cyclopropyl, and (C<sub>1</sub>-C<sub>4</sub>)alkyl. In certain embodiments, R<sup>3</sup> is phenyl substituted with 1 or 2 substituents independently selected from the group consisting of chloro, fluoro, and trifluoromethyl.

In certain embodiments, R<sup>3</sup> is benzyl optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, haloalkyl, alkyl, and cycloalkyl. In certain embodiments, R<sup>3</sup> is benzyl substituted with 1 or 2 substituents independently selected from the group consisting of chloro, fluoro, and trifluoromethyl. In certain embodiments, R<sup>3</sup> is benzyl substituted with 1, 2, or 3 substituents independently selected from the group consisting of chloro, fluoro, trifluoromethyl, cyclopropyl, and (C<sub>1</sub>-C<sub>4</sub>)alkyl.

In certain embodiments, R<sup>3</sup> is alkyl, hydroxyalkyl, or cycloalkyl, wherein said cycloalkyl is optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, haloalkyl, and hydroxyl. In certain embodiments, R<sup>3</sup> is alkyl or cycloalkyl, wherein said cycloalkyl is optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, haloalkyl, hydroxyl, and alkyl. In certain embodiments, R<sup>3</sup> is heteroaryl or heteroaralkyl, wherein said heteroaryl and heteroaralkyl are each optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, haloalkyl, and alkyl. In certain embodiments, R<sup>3</sup> is haloalkyl.

In certain embodiments, R<sup>5</sup> is hydrogen. In certain embodiments, R<sup>5</sup> is methyl.

In certain embodiments, R<sup>6</sup> is alkyl, haloalkyl, cyano, or aryl, wherein said aryl is optionally substituted with 1 or 2 substituents independently selected from the group consisting of halogen, haloalkyl, hydroxyl, and alkyl. In certain embodiments, R<sup>6</sup> is alkyl, haloalkyl, cyano, or aryl, wherein said aryl is optionally substituted with 1 or 2 substituents independently selected from the group consisting of halogen, haloalkyl, and alkyl. In certain embodiments, R<sup>6</sup> is haloalkyl. In certain embodiments, R<sup>6</sup> is trifluoromethyl. In certain embodiments, R<sup>6</sup> is phenyl optionally substituted with 1 or 2 substituents independently selected from the group consisting of chloro, fluoro, and hydroxyl. In certain embodiments, R<sup>6</sup> is phenyl optionally substituted with 1 or 2 substituents independently selected from the group consisting of chloro and fluoro.

In certain embodiments, R<sup>7</sup> is hydrogen. In certain embodiments, R<sup>7</sup> is trifluoromethyl.

In certain embodiments, R<sup>8</sup> represents independently for each occurrence hydrogen or methyl. In certain embodiments, R<sup>8</sup> is hydrogen.

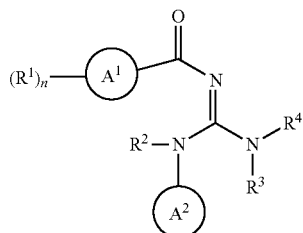
In certain embodiments, R<sup>9</sup> is alkyl, such as methyl or ethyl.

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In certain embodiments,  $R^{10}$  represents independently for each occurrence hydrogen or alkyl. In certain embodiments,  $R^{11}$  represents independently for each occurrence hydrogen or alkyl.

In certain embodiments,  $n$  is 1 or 2. In certain embodiments,  $n$  is 1. In certain embodiments,  $n$  is 2. In certain embodiments,  $m$  is 1 or 2.

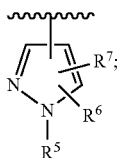
Another aspect of the invention provides a family of compounds represented by Formula I-A:



including all stereoisomers, geometric isomers, and tautomers; or a pharmaceutically acceptable salt or solvate of any of the foregoing; wherein:

$A^1$  is phenylene or a six-membered heteroarylene;

$A^2$  is



$R^1$  represents independently for each occurrence halogen, alkyl, haloalkyl, hydroxyl,  $C_1$ - $C_6$ alkoxy, or cyano;

$R^2$  is hydrogen or alkyl;

$R^3$  is aryl, aralkyl, cycloalkyl,  $-(C(R^8)_2)_m$ -cycloalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl,  $-(C(R^8)_2)_m$ -heterocycloalkyl, alkyl, haloalkyl, hydroxyalkyl,  $-(C(R^8)_2)_m$ -alkoxy, or  $-(C(R^8)_2)_m$ -CN, wherein said aryl, aralkyl, cycloalkyl, heteroaryl, heteroaralkyl, and heterocycloalkyl are each optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, haloalkyl, hydroxyl, alkyl, cycloalkyl,  $C_1$ - $C_6$ alkoxy, and cyano;

$R^4$  is hydrogen, alkyl, or  $-C(O)R^9$ ; or  $R^3$  and  $R^4$  are taken together with the nitrogen atom to which they are attached to form a 3 to 7 membered heterocyclic ring optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, haloalkyl, hydroxyl, alkyl, cycloalkyl, and  $C_1$ - $C_6$ alkoxy;

$R^5$  is hydrogen or alkyl;

$R^6$  is alkyl, cycloalkyl, haloalkyl, cyano, aryl, aralkyl, heteroaryl, or heteroaralkyl, wherein said cycloalkyl, aryl, aralkyl, heteroaryl, and heteroaralkyl are each optionally substituted with 1 or 2 substituents independently selected from the group consisting of halogen, haloalkyl, hydroxyl, alkyl,  $C_1$ - $C_6$ alkoxy, and cyano;

$R^7$  is hydrogen, alkyl, or haloalkyl;

$R^8$  represents independently for each occurrence hydrogen, alkyl, or cycloalkyl;

$R^9$  represents independently for each occurrence alkyl or cycloalkyl;

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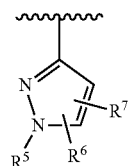
$n$  is 0, 1, 2, or 3; and

$m$  is 1, 2, 3, 4, or 5.

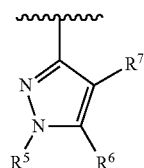
Definitions of the variables in Formula I-A above encompass multiple chemical groups. The application contemplates embodiments where, for example, i) the definition of a variable is a single chemical group selected from those chemical groups set forth above, ii) the definition is a collection of two or more of the chemical groups selected from those set forth above, and iii) the compound is defined by a combination of variables in which the variables are defined by (i) or (ii), e.g., such as where  $A^1$  is phenylene,  $R^1$  is halogen or haloalkyl,  $R^2$  is hydrogen, and  $R^4$  is hydrogen.

In certain embodiments, the compound is a compound of Formula I-A wherein  $A^1$  is phenylene. In certain embodiments,  $A^1$  is a six-membered heteroarylene, such as pyridinylene or pyrimidinylene. In certain embodiments,  $A^1$  is pyridinylene.

In certain embodiments,  $A^2$  is



In certain embodiments,  $A^2$  is



In certain embodiments,  $R^1$  is halogen or haloalkyl. In certain embodiments,  $R^1$  is chloro, fluoro, or trifluoromethyl.

In certain embodiments,  $R^2$  is hydrogen. In certain embodiments,  $R^2$  is alkyl, such as methyl or ethyl. In certain embodiments,  $R^4$  is hydrogen. In certain embodiments,  $R^4$  is alkyl, such as methyl or ethyl. In certain embodiments,  $R^2$  and  $R^4$  are hydrogen. In certain embodiments,  $R^4$  is  $-C(O)R^7$ . In certain embodiments,  $R^2$  and  $R^4$  are hydrogen.

In certain embodiments,  $R^3$  is aryl or aralkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, haloalkyl, alkyl, and cycloalkyl. In certain embodiments,  $R^3$  is phenyl optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, haloalkyl, alkyl, and cycloalkyl. In certain embodiments,  $R^3$  is phenyl substituted with 1, 2, or 3 substituents independently selected from the group consisting of chloro, fluoro, trifluoromethyl, cyclopropyl, and  $(C_1-C_4)$ alkyl. In certain embodiments,  $R^3$  is phenyl substituted with 1 or 2 substituents independently selected from the group consisting of chloro, fluoro, and trifluoromethyl.

In certain embodiments,  $R^3$  is benzyl optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, haloalkyl, alkyl, and cycloalkyl. In certain embodiments,  $R^3$  is benzyl substituted with 1 or 2 substituents independently selected from the group consisting of chloro, fluoro, and trifluoromethyl. In certain embodiments,  $R^3$  is benzyl substituted with 1, 2, or 3 substituents

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independently selected from the group consisting of chloro, fluoro, trifluoromethyl, cyclopropyl, and (C<sub>1</sub>-C<sub>4</sub>)alkyl.

In certain embodiments, R<sup>3</sup> is alkyl, hydroxyalkyl, or cycloalkyl, wherein said cycloalkyl is optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, haloalkyl, and hydroxyl. In certain embodiments, R<sup>3</sup> is alkyl or cycloalkyl, wherein said cycloalkyl is optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, haloalkyl, hydroxyl, and alkyl. In certain embodiments, R<sup>3</sup> is heteroaryl or heteroaralkyl, wherein said heteroaryl and heteroaralkyl are each optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, haloalkyl, and alkyl. In certain embodiments, R<sup>3</sup> is haloalkyl.

In certain embodiments, R<sup>5</sup> is hydrogen. In certain embodiments, R<sup>5</sup> is methyl.

In certain embodiments, R<sup>6</sup> is alkyl, haloalkyl, cyano, or aryl, wherein said aryl is optionally substituted with 1 or 2 substituents independently selected from the group consisting of halogen, haloalkyl, and alkyl. In certain embodiments, R<sup>6</sup> is haloalkyl. In certain embodiments, R<sup>6</sup> is trifluoromethyl. In certain embodiments, R<sup>6</sup> is phenyl optionally substituted with 1 or 2 substituents independently selected from the group consisting of chloro and fluoro.

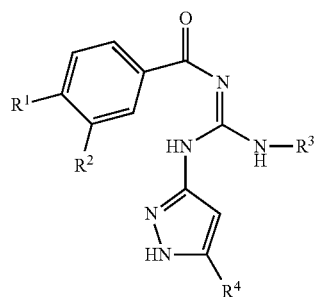
In certain embodiments, R<sup>7</sup> is hydrogen. In certain embodiments, R<sup>7</sup> is trifluoromethyl.

In certain embodiments, R<sup>8</sup> represents independently for each occurrence hydrogen or methyl. In certain embodiments, R<sup>8</sup> is hydrogen.

In certain embodiments, R<sup>9</sup> is alkyl, such as methyl or ethyl.

In certain embodiments, n is 1 or 2. In certain embodiments, n is 1. In certain embodiments, n is 2. In certain embodiments, m is 1 or 2.

Another aspect of the invention provides a family of compounds represented by Formula I-A1:



including all stereoisomers, geometric isomers, and tautomers; or a pharmaceutically acceptable salt or solvate of any of the foregoing; wherein:

R<sup>1</sup> and R<sup>2</sup> each represent independently for each occurrence hydrogen, chloro, fluoro, or —CF<sub>3</sub>;

R<sup>3</sup> is alkyl, cycloalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, or C<sub>1</sub>-C<sub>6</sub>alkylene-C<sub>1</sub>-C<sub>6</sub>alkoxy, wherein said cycloalkyl, aryl, aralkyl, heteroaryl, and heteroaralkyl are each optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, haloalkyl, hydroxyl, alkyl, C<sub>1</sub>-C<sub>6</sub>alkoxy, and cyano; and

R<sup>4</sup> is alkyl, cycloalkyl, haloalkyl, cyano, aryl, aralkyl, heteroaryl, or heteroaralkyl, wherein said cycloalkyl, aryl, aralkyl, heteroaryl, and heteroaralkyl are each optionally sub-

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stituted with 1 or 2 substituents independently selected from the group consisting of halogen, haloalkyl, hydroxyl, alkyl, C<sub>1</sub>-C<sub>6</sub>alkoxy, and cyano.

Definitions of the variables in Formula I-A1 above encompass multiple chemical groups. The application contemplates embodiments where, for example, i) the definition of a variable is a single chemical group selected from those chemical groups set forth above, ii) the definition is a collection of two or more of the chemical groups selected from those set forth above, and iii) the compound is defined by a combination of variables in which the variables are defined by (i) or (ii), e.g., such as where R<sup>1</sup> is chloro or fluoro; R<sup>3</sup> is aryl optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, haloalkyl, and alkyl; and R<sup>4</sup> is haloalkyl.

Accordingly, in certain embodiments, R<sup>1</sup> and R<sup>2</sup> are chloro or fluoro.

In certain embodiments, R<sup>3</sup> is alkyl or cycloalkyl. In certain embodiments, R<sup>3</sup> is C<sub>1</sub>-C<sub>6</sub>alkylene-C<sub>1</sub>-C<sub>6</sub>alkoxy. In certain embodiments, R<sup>3</sup> is aryl, aralkyl, heteroaryl, heteroaralkyl, or C<sub>1</sub>-C<sub>6</sub>alkylene-C<sub>1</sub>-C<sub>6</sub>alkoxy, wherein said aryl, aralkyl, heteroaryl, and heteroaralkyl are each optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, haloalkyl, hydroxyl, alkyl, C<sub>1</sub>-C<sub>6</sub>alkoxy, and cyano. In certain embodiments, R<sup>3</sup> is aryl or aralkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, haloalkyl, and alkyl. In certain embodiments, R<sup>3</sup> is phenyl optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of chloro, fluoro, trifluoromethyl, cyclopropyl, and (C<sub>1</sub>-C<sub>4</sub>)alkyl. In certain embodiments, R<sup>3</sup> is phenyl substituted with 1 or 2 substituents independently selected from the group consisting of chloro, fluoro, and trifluoromethyl.

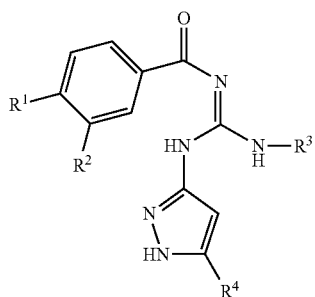
In certain embodiments, R<sup>3</sup> is benzyl optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, haloalkyl, and alkyl. In certain embodiments, R<sup>3</sup> is benzyl substituted with 1 or 2 substituents independently selected from the group consisting of chloro, fluoro, and trifluoromethyl. In certain embodiments, R<sup>3</sup> is benzyl substituted with 1, 2, or 3 substituents independently selected from the group consisting of chloro, fluoro, trifluoromethyl, cyclopropyl, and (C<sub>1</sub>-C<sub>4</sub>)alkyl. In certain embodiments, R<sup>3</sup> is alkyl or cycloalkyl, wherein said cycloalkyl is optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, haloalkyl, and alkyl.

In certain embodiments, R<sup>3</sup> is heteroaryl or heteroaralkyl, wherein said heteroaryl and heteroaralkyl are each optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, haloalkyl, and alkyl. In certain embodiments, R<sup>3</sup> is haloalkyl.

In certain embodiments, R<sup>4</sup> is alkyl, haloalkyl, cyano, or aryl, wherein said aryl is optionally substituted with 1 or 2 substituents independently selected from the group consisting of halogen, haloalkyl, and alkyl. In certain embodiments, R<sup>4</sup> is haloalkyl. In certain embodiments, R<sup>4</sup> is trifluoromethyl. In certain embodiments, R<sup>4</sup> is phenyl optionally substituted with 1 or 2 substituents independently selected from the group consisting of chloro, fluoro, and hydroxyl. In certain embodiments, R<sup>4</sup> is phenyl optionally substituted with 1 or 2 substituents independently selected from the group consisting of chloro and fluoro.

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Another aspect of the invention provides a family of compounds represented by Formula I-B:



or a pharmaceutically acceptable salt thereof; wherein:

R<sup>1</sup> and R<sup>2</sup> each represent independently for each occurrence hydrogen, chloro, fluoro, or —CF<sub>3</sub>;

R<sup>3</sup> is aryl, aralkyl, heteroaryl, or heteroaralkyl, wherein said aryl, aralkyl, heteroaryl, and heteroaralkyl are each optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, haloalkyl, and alkyl; and

R<sup>4</sup> is alkyl, cycloalkyl, haloalkyl, cyano, aryl, aralkyl, heteroaryl, or heteroaralkyl, wherein said cycloalkyl, aryl, aralkyl, heteroaryl, and heteroaralkyl are each optionally substituted with 1 or 2 substituents independently selected from the group consisting of halogen, haloalkyl, and alkyl.

Definitions of the variables in Formulae I-B above encompass multiple chemical groups. The application contemplates embodiments where, for example, i) the definition of a variable is a single chemical group selected from those chemical groups set forth above, ii) the definition is a collection of two or more of the chemical groups selected from those set forth above, and iii) the compound is defined by a combination of variables in which the variables are defined by (i) or (ii), e.g., such as where R<sup>1</sup> is chloro or fluoro; R<sup>3</sup> is aryl optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, haloalkyl, and alkyl; and R<sup>4</sup> is haloalkyl.

Accordingly, in certain embodiments, R<sup>1</sup> and R<sup>2</sup> are chloro or fluoro.

In certain embodiments, R<sup>3</sup> is aryl or aralkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, haloalkyl, and alkyl. In certain embodiments, R<sup>3</sup> is phenyl optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, haloalkyl, and alkyl. In certain embodiments, R<sup>3</sup> is phenyl substituted with 1, 2, or 3 substituents independently selected from the group consisting of chloro, fluoro, trifluoromethyl, cyclopropyl, and (C<sub>1</sub>-C<sub>4</sub>)alkyl. In certain embodiments, R<sup>3</sup> is phenyl substituted with 1 or 2 substituents independently selected from the group consisting of chloro, fluoro, and trifluoromethyl.

In certain embodiments, R<sup>3</sup> is benzyl optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, haloalkyl, and alkyl. In certain embodiments, R<sup>3</sup> is benzyl substituted with 1 or 2 substituents independently selected from the group consisting of chloro, fluoro, and trifluoromethyl. In certain embodiments, R<sup>3</sup> is benzyl substituted with 1, 2, or 3 substituents independently selected from the group consisting of chloro, fluoro, trifluoromethyl, cyclopropyl, and (C<sub>1</sub>-C<sub>4</sub>)alkyl. In certain

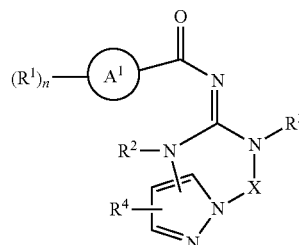
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embodiments, R<sup>3</sup> is alkyl or cycloalkyl, wherein said cycloalkyl is optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, haloalkyl, and alkyl.

In certain embodiments, R<sup>3</sup> is heteroaryl or heteroaralkyl, wherein said heteroaryl and heteroaralkyl are each optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, haloalkyl, and alkyl. In certain embodiments, R<sup>3</sup> is haloalkyl.

In certain embodiments, R<sup>4</sup> is alkyl, haloalkyl, cyano, or aryl, wherein said aryl is optionally substituted with 1 or 2 substituents independently selected from the group consisting of halogen, haloalkyl, and alkyl. In certain embodiments, R<sup>4</sup> is haloalkyl. In certain embodiments, R<sup>4</sup> is trifluoromethyl. In certain embodiments, R<sup>4</sup> is phenyl optionally substituted with 1 or 2 substituents independently selected from the group consisting of chloro and fluoro.

Another aspect of the invention provides a family of compounds represented by Formula II:



including all stereoisomers, geometric isomers, and tautomers; or a pharmaceutically acceptable salt or solvate of any of the foregoing; wherein:

A<sup>1</sup> is phenylene or a six-membered heteroarylene;

X is —[C(R<sup>5</sup>)<sub>2</sub>]<sub>m</sub> or —[C(R<sup>5</sup>)<sub>2</sub>]<sub>p</sub>—C(O)—[C(R<sup>5</sup>)<sub>2</sub>]<sub>p</sub>;

R<sup>1</sup> represents independently for each occurrence halogen, haloalkyl, alkyl, cycloalkyl, heterocycloalkyl, hydroxyl, C<sub>1</sub>-C<sub>6</sub>alkoxy, cyano, —CO<sub>2</sub>R<sup>6</sup>, —C(O)R<sup>7</sup>, —S(O)R<sup>7</sup>, —SO<sub>2</sub>R<sup>7</sup>, —SO<sub>2</sub>N(R<sup>8</sup>)(R<sup>9</sup>), —C(O)N(R<sup>8</sup>)(R<sup>9</sup>), —N(R<sup>8</sup>)(R<sup>9</sup>), or —N(R<sup>6</sup>)C(O)(R<sup>7</sup>);

R<sup>2</sup> is hydrogen or alkyl;

R<sup>3</sup> is hydrogen, aryl, aralkyl, cycloalkyl, —(C(R<sup>6</sup>)<sub>2</sub>)<sub>m</sub>-cycloalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, —(C(R<sup>6</sup>)<sub>2</sub>)<sub>m</sub>-heterocycloalkyl, alkyl, haloalkyl, hydroxyalkyl, —(C(R<sup>6</sup>)<sub>2</sub>)<sub>m</sub>-alkoxy, —(C(R<sup>6</sup>)<sub>2</sub>)<sub>m</sub>-O—(C(R<sup>6</sup>)<sub>2</sub>)<sub>m</sub>-alkoxy, or —(C(R<sup>6</sup>)<sub>2</sub>)<sub>m</sub>-CN, wherein said aryl, aralkyl, cycloalkyl, heteroaryl, heteroaralkyl, and heterocycloalkyl are each optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, haloalkyl, hydroxyl, alkyl, cycloalkyl, hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>alkoxy, cyano, and —C<sub>1</sub>-C<sub>6</sub>alkylene-CO<sub>2</sub>R<sup>6</sup>; or R<sup>3</sup> and a single occurrence of R<sup>5</sup> are taken together with the atoms to which they are attached to form a saturated heterocyclic ring;

R<sup>4</sup> is alkyl, cycloalkyl, haloalkyl, cyano, aryl, aralkyl, heteroaryl, heteroaralkyl, —CO<sub>2</sub>R<sup>6</sup>, or —C(O)N(R<sup>8</sup>)(R<sup>9</sup>), wherein said cycloalkyl, aryl, aralkyl, heteroaryl, and heteroaralkyl are each optionally substituted with 1 or 2 substituents independently selected from the group consisting of halogen, haloalkyl, hydroxyl, alkyl, hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>alkoxy, —O-aralkyl, and cyano;

R<sup>5</sup> represents independently for each occurrence hydrogen or alkyl; or R<sup>3</sup> and a single occurrence of R<sup>5</sup> are taken together with the atoms to which they are attached to form a saturated heterocyclic ring;

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R<sup>6</sup> represents independently for each occurrence hydrogen, alkyl, or cycloalkyl; or two occurrences of R<sup>6</sup> attached to the same carbon atom are taken together with said carbon atom to form a saturated carbocyclic ring;

R<sup>7</sup> represents independently for each occurrence alkyl or cycloalkyl;

R<sup>8</sup> and R<sup>9</sup> each represent independently for each occurrence hydrogen, alkyl, or cycloalkyl; or R<sup>8</sup> and R<sup>9</sup> are taken together with the nitrogen atom to which they are attached to form a 3 to 7 membered heterocyclic ring optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, haloalkyl, hydroxyl, alkyl, cycloalkyl, and C<sub>1</sub>-C<sub>6</sub>alkoxy;

n is 0, 1, 2, or 3;

m represents independently for each occurrence 1, 2, 3, 4, or 5; and

p represents independently for each occurrence 0, 1, or 2.

Definitions of the variables in Formulae II above encompass multiple chemical groups. The application contemplates embodiments where, for example, i) the definition of a variable is a single chemical group selected from those chemical groups set forth above, ii) the definition is a collection of two or more of the chemical groups selected from those set forth above, and iii) the compound is defined by a combination of variables in which the variables are defined by (i) or (ii), e.g., such as where R<sup>1</sup> is halogen or haloalkyl; R<sup>3</sup> is aryl optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, haloalkyl, and alkyl; and R<sup>4</sup> is haloalkyl.

Accordingly, in certain embodiments, A<sup>1</sup> is phenylene.

In certain embodiments, X is —[C(R<sup>5</sup>)<sub>2</sub>]<sub>m</sub>. In certain other embodiments, X is —C(O)—.

In certain embodiments, R<sup>1</sup> is halogen.

In certain embodiments, R<sup>3</sup> is hydrogen or aralkyl optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, haloalkyl, hydroxyl, and alkyl.

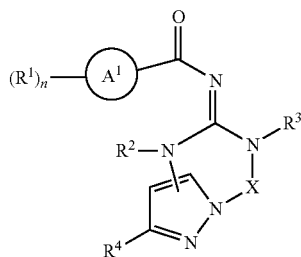
In certain embodiments, R<sup>4</sup> is alkyl, haloalkyl, or aryl, wherein said aryl is optionally substituted with 1 or 2 substituents independently selected from the group consisting of halogen, haloalkyl, and alkyl. In certain embodiments, R<sup>4</sup> is trifluoromethyl. In certain embodiments, R<sup>4</sup> is phenyl optionally substituted with 1 or 2 substituents independently selected from the group consisting of chloro and fluoro.

In certain embodiments, R<sup>5</sup> is hydrogen.

In certain embodiments, n is 1 or 2.

In certain embodiments, m is 0.

Another aspect of the invention provides a family of compounds represented by Formula II-A:



(II-A)

including all stereoisomers, geometric isomers, and tautomers; or a pharmaceutically acceptable salt or solvate of any of the foregoing; wherein:

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A<sup>1</sup> is phenylene or a six-membered heteroarylene;

X is —[C(R<sup>5</sup>)<sub>2</sub>]<sub>m</sub> or —[C(R<sup>5</sup>)<sub>2</sub>]<sub>p</sub>—C(O)—[C(R<sup>5</sup>)<sub>2</sub>]<sub>p</sub>;

R<sup>1</sup> represents independently for each occurrence halogen, haloalkyl, alkyl, cycloalkyl, heterocycloalkyl, hydroxyl, C<sub>1</sub>-C<sub>6</sub>alkoxy, cyano, —CO<sub>2</sub>R<sup>6</sup>, —C(O)R<sup>7</sup>, —SO<sub>2</sub>R<sup>7</sup>, —SO<sub>2</sub>N(R<sup>8</sup>)(R<sup>9</sup>), —C(O)N(R<sup>8</sup>)(R<sup>9</sup>), —N(R<sup>8</sup>)(R<sup>9</sup>), or —N(R<sup>6</sup>)C(O)(R<sup>7</sup>);

R<sup>2</sup> is hydrogen or alkyl;

R<sup>3</sup> is hydrogen, aryl, aralkyl, cycloalkyl, —(C(R<sup>6</sup>)<sub>2</sub>)<sub>m</sub>-cycloalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, —(C(R<sup>6</sup>)<sub>2</sub>)<sub>m</sub>-heterocycloalkyl, alkyl, haloalkyl, hydroxyalkyl, —(C(R<sup>6</sup>)<sub>2</sub>)<sub>m</sub>-alkoxy, —(C(R<sup>6</sup>)<sub>2</sub>)<sub>m</sub>-O—(C(R<sup>6</sup>)<sub>2</sub>)<sub>m</sub>-alkoxy, or —(C(R<sup>6</sup>)<sub>2</sub>)<sub>m</sub>—CN, wherein said aryl, aralkyl, cycloalkyl, heteroaryl, heteroaralkyl, and heterocycloalkyl

are each optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, haloalkyl, hydroxyl, alkyl, cycloalkyl, hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>alkoxy, cyano, and —C<sub>1</sub>-C<sub>6</sub>alkylene-CO<sub>2</sub>R<sup>6</sup>; or R<sup>3</sup> and a single occurrence of R<sup>5</sup> are taken together with the atoms to which they are attached to form a saturated heterocyclic ring;

R<sup>4</sup> is alkyl, cycloalkyl, haloalkyl, cyano, aryl, aralkyl, heteroaryl, heteroaralkyl, —CO<sub>2</sub>R<sup>6</sup>, or —C(O)N(R<sup>8</sup>)(R<sup>9</sup>), wherein said cycloalkyl, aryl, aralkyl, heteroaryl, and heteroaralkyl are each optionally substituted with 1 or 2 substituents independently selected from the group consisting of halogen, haloalkyl, hydroxyl, alkyl, hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>alkoxy, and cyano;

R<sup>5</sup> represents independently for each occurrence hydrogen or alkyl; or R<sup>3</sup> and a single occurrence of R<sup>5</sup> are taken together with the atoms to which they are attached to form a saturated heterocyclic ring;

R<sup>6</sup> represents independently for each occurrence hydrogen, alkyl, or cycloalkyl; or two occurrences of R<sup>6</sup> attached to the same carbon atom are taken together with said carbon atom to form a saturated carbocyclic ring;

R<sup>7</sup> represents independently for each occurrence alkyl or cycloalkyl;

R<sup>8</sup> and R<sup>9</sup> each represent independently for each occurrence hydrogen, alkyl, or cycloalkyl; or R<sup>8</sup> and R<sup>9</sup> are taken together with the nitrogen atom to which they are attached to form a 3 to 7 membered heterocyclic ring optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, haloalkyl, hydroxyl, alkyl, cycloalkyl, and C<sub>1</sub>-C<sub>6</sub>alkoxy;

n is 0, 1, 2, or 3;

m represents independently for each occurrence 1, 2, 3, 4, or 5; and

p represents independently for each occurrence 0, 1, or 2.

Definitions of the variables in Formulae II-A above encompass multiple chemical groups. The application contemplates embodiments where, for example, i) the definition of a variable is a single chemical group selected from those chemical groups set forth above, ii) the definition is a collection of two or more of the chemical groups selected from those set forth above, and iii) the compound is defined by a combination of variables in which the variables are defined by (i) or (ii), e.g., such as where R<sup>1</sup> is halogen or haloalkyl; R<sup>3</sup> is aryl optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, haloalkyl, and alkyl; and R<sup>4</sup> is haloalkyl. In certain other embodiments, variables A<sup>1</sup>, X, R<sup>1</sup> through R<sup>9</sup>, n, m, and/or p for Formula II-A are as defined by one of the further embodiments specified above in connection with Formula II.

Further, the description above describes multiple embodiments providing definitions for variables used herein. The application specifically contemplates all combinations of such embodiments. For example, the application contemplates particular combinations of embodiments relating to

## 25

Formula I-A, such as where A<sup>1</sup> is phenylene, R<sup>1</sup> is halogen or haloalkyl, and n is 1. Further, for example, the application contemplates particular combinations of embodiments relating to Formula I-A1, such as where R<sup>1</sup> and R<sup>2</sup> are independently chloro or fluoro, and R<sup>3</sup> is phenyl substituted with 1 or 2 substituents independently selected from the group consisting of chloro, fluoro, and trifluoromethyl.

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In certain embodiments, the compound is one of the compounds listed in any one of Tables 1-4 below, or a pharmaceutically acceptable salt thereof. In certain other embodiments, the compound is one of the compounds listed in Table 1 below, or a pharmaceutically acceptable salt thereof. It is understood that the foregoing compounds can be combined with a pharmaceutically acceptable carrier to produce a pharmaceutical composition.

TABLE 1

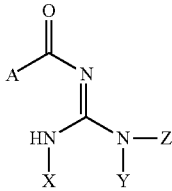
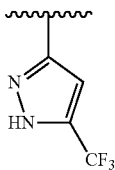
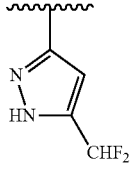
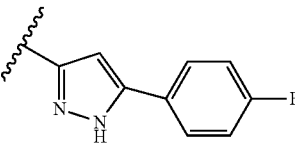
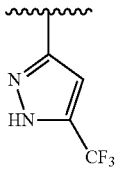
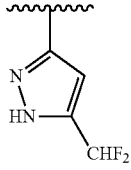
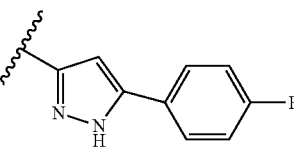
				
No.	A	X	Y	Z
I-1	3-chlorophenyl		H	3-chlorophenyl
I-2	4-chlorophenyl		H	4-chlorophenyl
I-3	3-fluorophenyl		H	3,5-dichlorophenyl
I-4	4-fluorophenyl		H	3-chloro-4-fluorophenyl
I-5	3,4-dichlorophenyl		H	3-chloro-5-fluorophenyl
I-6	3,4-difluorophenyl		H	3-trifluoromethylphenyl

TABLE 1-continued

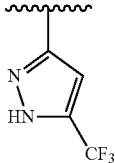
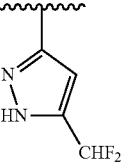
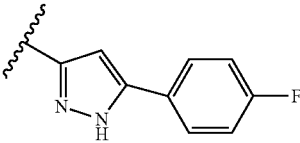
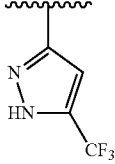
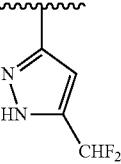
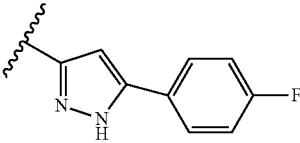
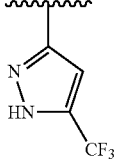
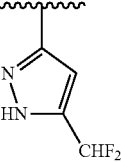
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No.	A	X	Y	Z
I-7	4-trifluoromethylphenyl		H	3-cyclopropylphenyl
I-8	3-chlorophenyl		H	3-tert-butylphenyl
I-9	4-chlorophenyl		H	2-cyclopropylphenyl
I-10	3-fluorophenyl		H	2-cyclopropyl-4-fluorophenyl
I-11	4-fluorophenyl		H	3-chlorobenzyl
I-12	3,4-dichlorophenyl		H	4-chlorobenzyl
I-13	3,4-difluorophenyl		H	3-fluorobenzyl
I-14	4-trifluoromethylphenyl		H	4-fluorobenzyl



TABLE 1-continued

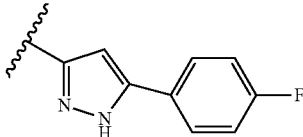
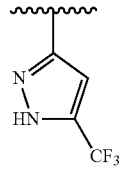
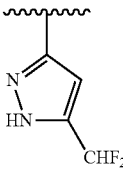
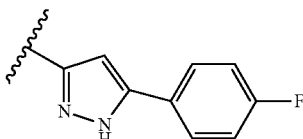
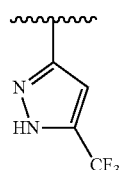
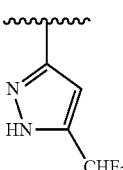
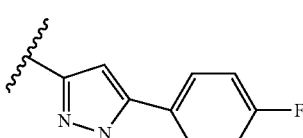
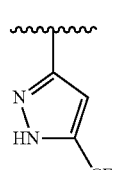
$  \begin{array}{c}  \text{O} \\  \parallel \\  \text{A}-\text{C}=\text{N} \\  \parallel \\  \text{HN}-\text{C}=\text{N}-\text{Z} \\    \quad   \\  \text{X} \quad \text{Y}  \end{array}  $				
No.	A	X	Y	Z
I-15	3-chlorophenyl		H	3-chloro-5-fluorobenzyl
I-16	4-chlorophenyl		H	3,5-dichlorobenzyl
I-17	3-fluorophenyl		H	3,5-difluorobenzyl
I-18	4-fluorophenyl		H	3-cyclopropylbenzyl
I-19	3,4-dichlorophenyl		H	3-trifluoromethylbenzyl
I-20	3,4-difluorophenyl		H	4-trifluoromethylbenzyl
I-21	4-trifluoromethylphenyl		H	cyclopropyl
I-22	3-chlorophenyl		H	cyclopentyl

TABLE 1-continued

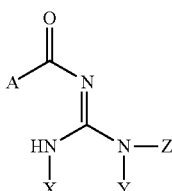
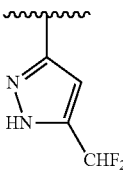
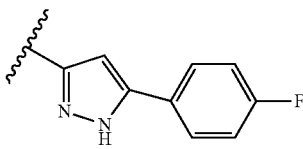
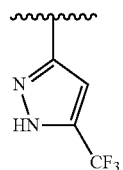
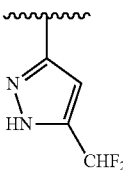
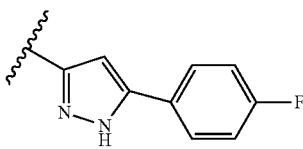
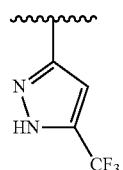
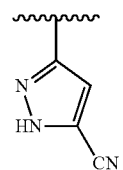
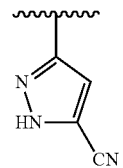
				
No.	A	X	Y	Z
I-23	4-chlorophenyl		H	cyclohexyl
I-24	3-fluorophenyl		H	4-methylcyclohexyl
I-25	4-fluorophenyl		H	ethyl
I-26	3,4-dichlorophenyl		H	tert-butyl
I-27	3,4-difluorophenyl		H	2,2,2-trifluoroethyl
I-28	4-trifluoromethylphenyl		H	1-methylcyclobutyl
I-29	3-chlorophenyl		H	3-chloro-4-fluorophenyl
I-30	4-chlorophenyl		H	3-chloro-5-fluorophenyl

TABLE 1-continued

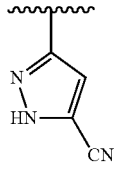
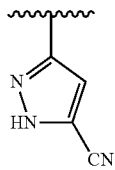
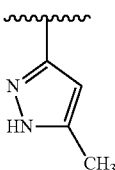
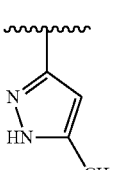
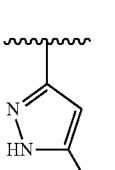
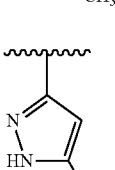
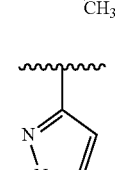
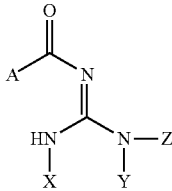
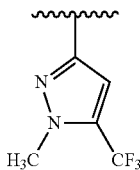
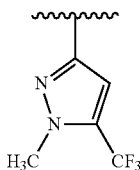
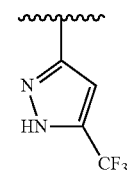
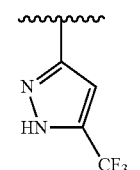
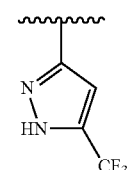
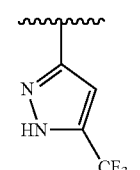
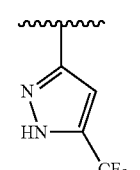
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No.	A	X	Y	Z
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I-32	4-fluorophenyl		H	4-chlorophenyl
I-33	3,4-dichlorophenyl		H	3,5-dichlorophenyl
I-34	3,4-difluorophenyl		H	3-chloro-4-fluorophenyl
I-35	4-trifluoromethylphenyl		H	3-chloro-5-fluorophenyl
I-36	3-chlorophenyl		H	3-trifluoromethylphenyl
I-37	4-chlorophenyl		H	3-chlorophenyl

TABLE 1-continued

				
No.	A	X	Y	Z
I-38	3-fluorophenyl		H	4-chlorophenyl
I-39	4-fluorophenyl		H	3,5-dichlorophenyl
I-40	3-chlorophenyl		—C(O)Me	3-chlorophenyl
I-41	4-chlorophenyl		—C(O)Me	4-chlorophenyl
I-42	3-trifluorophenyl		—C(O)Me	3-chloro-4-fluorophenyl
I-43	3-fluorophenyl		—CH <sub>3</sub>	3-chlorophenyl
I-44	4-fluorophenyl		—CH <sub>3</sub>	4-chlorophenyl

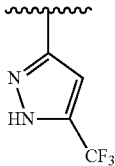
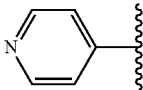
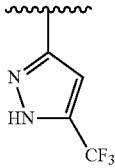
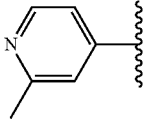
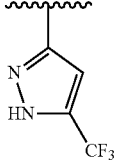
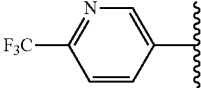
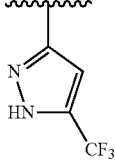
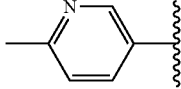
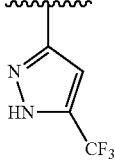
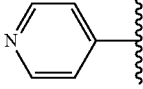
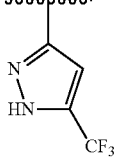
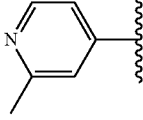
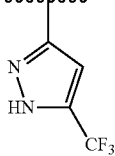
No.	A	X	Y	Z
I-45	3-trifluorophenyl		—CH <sub>3</sub>	3-chloro-4-fluorophenyl
I-46			H	4-chlorophenyl
I-47			H	3-chloro-4-fluorophenyl
I-48			H	4-chlorophenyl
I-49			H	3-chloro-4-fluorophenyl
I-50			H	4-chlorophenyl
I-51			H	3-chloro-4-fluorophenyl

TABLE 1-continued

$  \begin{array}{c}  \text{O} \\  \parallel \\  \text{A}-\text{C}-\text{N} \\  \parallel \\  \text{HN}-\text{C}-\text{N}-\text{Z} \\    \quad   \\  \text{X} \quad \text{Y}  \end{array}  $				
No.	A	X	Y	Z
I-52			H	4-chlorophenyl
I-53			H	3-chloro-4-fluorophenyl
I-54			H	4-chlorophenyl
I-55			H	3-chloro-4-fluorophenyl
I-56	4-trifluoromethylphenyl		H	tert-butyl
I-57			H	tert-butyl
I-58			H	tert-butyl

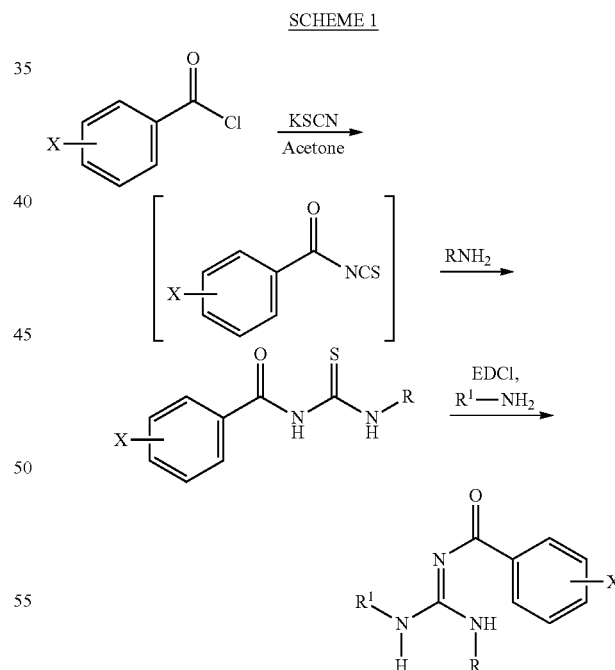
TABLE 1-continued

$  \begin{array}{c}  \text{O} \\  \parallel \\  \text{A}-\text{C}=\text{N} \\  \parallel \\  \text{HN}-\text{C}-\text{N}-\text{Z} \\    \quad   \\  \text{X} \quad \text{Y}  \end{array}  $				
No.	A	X	Y	Z
I-59			H	
I-60			H	tert-butyl

In certain other embodiments, the compound is one of the compounds listed in Examples 1-18, or a pharmaceutically acceptable salt of said compounds. It is understood that the foregoing compounds can be combined with a pharmaceutically acceptable carrier to produce a pharmaceutical composition.

Exemplary methods for preparing compounds described herein are provided in the examples. Further exemplary procedures for making various compounds described herein are described in Scheme 1 below. The synthetic scheme is provided for the purpose of illustrating the invention, but not for limiting the scope or spirit of the invention. Starting materials can be obtained from commercial sources or be prepared based on procedures described in the literature.

The synthetic route in Scheme 1 involves reacting an optionally substituted benzoylchloride with potassium thiocyanate to form an acyl isothiocyanate intermediate. This acyl isothiocyanate intermediate is treated with an amino-pyrazole compound to form an acyl thiourea. The acyl thiourea is reacted with 1-ethyl-2',2'-dimethylaminopropylcarbodiimide (EDCI) and a second amine compound (e.g., an aniline or benzylamine) to form the desired pyrazolyl guanidine compound. To the extent either the amino-pyrazole or the second amine compound contain a further functional group that may undergo reaction under the conditions illustrated in Scheme 1, standard protecting group strategies for protection and deprotection may be employed. See, for example, Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2<sup>nd</sup> ed.; Wiley: New York, 1991. It is understood that the optionally substituted benzoylchloride starting material can be replaced with a heteroaryl acid chloride (i.e., nicotinoyl chloride) to prepare pyrazolyl guanidines containing a —C(O)-heteroaryl moiety.



### III. Therapeutic Applications of Pyrazolyl Guanidine Compounds

It is contemplated that the guanidine compounds described herein, such as the guanidine compounds of Formula I, I-A, I-A1, I-B, II and II-A, provide therapeutic benefits to patients suffering from any one or more of a number of conditions, e.g., diseases characterized by dysregulation of F<sub>1</sub>F<sub>0</sub>-ATPase activity, diseases characterized by dysregulation of necrosis

and/or apoptosis processes in a cell or tissue, disease characterized by aberrant cell growth and/or hyperproliferation. The compounds described herein can also be used to treat a variety of dysregulatory disorders related to cellular death as described elsewhere herein. Additionally, the compounds described herein can be used to inhibit ATP synthesis.

Accordingly, one aspect of the invention provides a method of treating a subject suffering from a medical disorder. The method comprises administering to the subject a therapeutically effective amount of one or more pyrazolyl guanidine compounds described herein, e.g., a compound of Formula I, I-A, I-A1, I-B, II, or II-A, as described in Section II above, in order to ameliorate a symptom of the disorder.

A large number of medical disorders can be treated using the guanidine compounds described herein. For example, the compounds described herein can be used to treat medical disorders characterized by dysregulation of necrosis and/or apoptosis processes in a cell or tissue, diseases characterized by aberrant cell growth and/or hyperproliferation, etc., or lupus, rheumatoid arthritis, psoriasis, graft-versus-host disease, Crohn's disease, inflammatory bowel disease, multiple sclerosis, cardiovascular disease, myeloma, lymphoma, cancer, and bacterial infection. In certain embodiments, the cancer is a solid tumor, leukemia, colon cancer, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, lung cancer, small cell lung cancer, non-small cell lung cancer, bladder cancer, stomach cancer, cervical cancer, testicular tumor, skin cancer, rectal cancer, thyroid cancer, kidney cancer, uterus cancer, esophagus cancer, liver cancer, an acoustic neuroma, oligodendroglioma, meningioma, melanoma, neuroblastoma, or retinoblastoma.

Although not wishing to be bound to a particular theory, it is believed that the compounds impart therapeutic benefit by modulating (e.g., inhibiting or promoting) the activity of the  $F_1F_0$ -ATPase complexes (e.g., mitochondrial  $F_1F_0$ -ATPase complexes) in affected cells or tissues. In some embodiments, the compositions of the present invention are used to treat immune/chronic inflammatory conditions (e.g., psoriasis, autoimmune disorders, organ-transplant rejection, and epidermal hyperplasia). In further embodiments, the compositions of the present invention are used in conjunction with stenosis therapy to treat compromised (e.g., occluded) vessels.

In certain embodiments, a composition comprising a guanidine compound is administered under conditions (e.g., timing, dose, co-administration with other agent, mode of administration, selection of subject, use of targeting agents, etc.) that maximize desired effects directed at the  $F_1F_0$ -ATPase.

In certain embodiments, the medical disorder is an immune disorder. In certain other embodiments, the medical disorder is an inflammatory disorder. In certain other embodiments, the medical disorder is an autoimmune disorder. In certain other embodiments, the medical disorder is rheumatoid arthritis, psoriasis, chronic graft-versus-host disease, acute graft-versus-host disease, Crohn's disease, inflammatory bowel disease, multiple sclerosis, systemic lupus erythematosus, Celiac Sprue, idiopathic thrombocytopenic thrombotic purpura, myasthenia gravis, Sjogren's syndrome, scleroderma, ulcerative colitis, asthma, uveitis, or epidermal hyperplasia.

In certain other embodiments, the medical disorder is cartilage inflammation, bone degradation, arthritis, juvenile arthritis, juvenile rheumatoid arthritis, pauciarticular juvenile rheumatoid arthritis, polyarticular juvenile rheumatoid

arthritis, systemic onset juvenile rheumatoid arthritis, juvenile ankylosing spondylitis, juvenile enteropathic arthritis, juvenile reactive arthritis, juvenile Reter's Syndrome, SEA Syndrome, juvenile dermatomyositis, juvenile psoriatic arthritis, juvenile scleroderma, juvenile systemic lupus erythematosus, juvenile vasculitis, pauciarticular rheumatoid arthritis, polyarticular rheumatoid arthritis, systemic onset rheumatoid arthritis, ankylosing spondylitis, enteropathic arthritis, reactive arthritis, Reter's Syndrome, dermatomyositis, psoriatic arthritis, vasculitis, myolitis, polymyolitis, dermatomyolitis, osteoarthritis, polyarteritis nodosa, Wegener's granulomatosis, arteritis, polymyalgia rheumatica, sarcoidosis, sclerosis, primary biliary sclerosis, sclerosing cholangitis, dermatitis, atopic dermatitis, atherosclerosis, Still's disease, chronic obstructive pulmonary disease, Guillain-Barre disease, Type I diabetes mellitus, Graves' disease, Addison's disease, Raynaud's phenomenon, or autoimmune hepatitis. In certain embodiments, the psoriasis is plaque psoriasis, guttate psoriasis, inverse psoriasis, pustular psoriasis, or erythrodermic psoriasis.

In certain other embodiments, the medical disorder is Crohn's disease, inflammatory bowel disease, multiple sclerosis, graft-versus-host disease, lupus, rheumatoid arthritis, or psoriasis. In certain other embodiments, the medical disorder is cardiovascular disease, myeloma, lymphoma, or cancer. In certain other embodiments, the medical disorder is lupus, rheumatoid arthritis, psoriasis, graft-versus-host disease, myeloma, or lymphoma. In certain other embodiments, the medical disorder is cardiovascular disease or cancer. In certain other embodiments, the medical disorder is Crohn's disease, inflammatory bowel disease, or multiple sclerosis. In certain other embodiments, the medical disorder is graft-versus-host disease. In further embodiments, the medical disorder is a bacterial infection. In certain embodiments, the patient (or subject) is a human.

As indicated above, the guanidine compounds described herein can be used in the treatment of a bacterial infection. A variety of bacteria are contemplated to be susceptible to the guanidine compounds. Representative bacteria include *Staphylococci* species, e.g., *S. aureus*; *Enterococci* species, e.g., *E. faecalis* and *E. faecium*; *Streptococci* species, e.g., *S. pyogenes* and *S. pneumoniae*; *Escherichia* species, e.g., *E. coli*, including enterotoxigenic, enteropathogenic, enteroinvasive, enterohemorrhagic and enteroaggregative *E. coli* strains; *Haemophilus* species, e.g., *H. influenzae*; and *Moraxella* species, e.g., *M. catarrhalis*. Other examples include *Mycobacteria* species, e.g., *M. tuberculosis*, *M. avian-intracellulare*, *M. kansasii*, *M. Bovis*, *M. africanum*, *M. genavense*, *M. leprae*, *M. xenopi*, *M. simiae*, *M. scrofulaceum*, *M. malmoense*, *M. celatum*, *M. abscessus*, *M. chelonae*, *M. szulgai*, *M. gordonae*, *M. haemophilum*, *M. fortuni* and *M. marinum*; *Corynebacteria* species, e.g., *C. diphtheriae*; *Vibrio* species, e.g., *V. cholerae*; *Campylobacter* species, e.g., *C. jejuni*; *Helicobacter* species, e.g., *H. pylori*; *Pseudomonas* species, e.g., *P. aeruginosa*; *Legionella* species, e.g., *L. pneumophila*; *Treponema* species, e.g., *T. pallidum*; *Borrelia* species, e.g., *B. burgdorferi*; *Listeria* species, e.g., *L. monocytogenes*; *Bacillus* species, e.g., *B. cereus*; *Bordetella* species, e.g., *B. pertussis*; *Clostridium* species, e.g., *C. perfringens*, *C. tetani*, *C. difficile* and *C. botulinum*; *Neisseria* species, e.g., *N. meningitidis* and *N. gonorrhoeae*; *Chlamydia* species, e.g., *C. psittaci*, *C. pneumoniae* and *C. trachomatis*; *Rickettsia* species, e.g., *R. rickettsii* and *R. prowazekii*; *Shigella* species, e.g., *S. sonnei*; *Salmonella* species, e.g., *S. typhimurium*; *Yersinia* species, e.g., *Y. enterocolitica* and *Y. pseudotuberculosis*; *Klebsiella* species, e.g., *K. pneumoniae*; *Mycoplasma* species, e.g., *M. pneumoniae*; and *Trypanosoma brucei*. In



certain embodiments, the guanidine compounds described herein are used to treat a subject suffering from a bacterial infection selected from the group consisting of *S. aureus*, *E. faecalis*, *E. faecium*, *S. pyogenes*, *S. pneumoniae*, and *P. aeruginosa*. In certain embodiments, the guanidine compounds described herein are used to treat a subject suffering from a *Trypanosoma brucei* infection.

The antibacterial activity of the compounds described herein may be evaluated using standard assays known in the art, such as the microbroth dilution minimum inhibition concentration (MIC) assay, as further described in National Committee for Clinical Laboratory Standards. Performance Standards for Antimicrobial Susceptibility Testing; Fourteenth Informational Supplement. NCCLS document M100-S14 [ISBN 1-56238-5,6-X]. This assay may be used to determine the minimum concentration of a compound necessary to prevent visible bacterial growth in a solution. In general, the drug to be tested is serially diluted into wells, and aliquots of liquid bacterial culture are added. This mixture is incubated under appropriate conditions, and then tested for growth of the bacteria. Compounds with low or no antibiotic activity (a high MIC) will allow growth at high concentrations of compound, while compounds with high antibiotic activity will allow bacterial growth only at lower concentrations (a low MIC).

The assay uses stock bacterial culture conditions appropriate for the chosen strain of bacteria. Stock cultures from the permanent stock culture collection can be stored as frozen suspensions at  $-70^{\circ}\text{C}$ . Cultures may be suspended in 10% skim milk (BD) prior to snap freezing in dry ice/ethanol and then placed in a  $-70^{\circ}\text{C}$ . freezer. Cultures may be maintained on Tryptic Soy Agar containing 5% Sheep Blood at room temperature ( $20^{\circ}\text{C}$ .), and each culture may be recovered from frozen form and transferred an additional time before MIC testing. Fresh plates are inoculated the day before testing, incubated overnight, and checked to confirm purity and identity.

The identity and purity of the cultures recovered from the stock culture can be confirmed to rule out the possibility of contamination. The identity of the strains may be confirmed by standard microbiological methods (See, e.g., Murray et al., Manual of Clinical Microbiology, Eighth Edition. ASM Press [ISBN 1-55581-255-4]). In general, cultures are streaked onto appropriate agar plates for visualization of purity, expected colony morphology, and hemolytic patterns. Gram stains can also be utilized. The identities are confirmed using a MicroScan WalkAway 40 SI Instrument (Dade Behring, West Sacramento, Calif.). This device utilizes an automated incubator, reader, and computer to assess for identification purposes the biochemical reactions carried out by each organism. The MicroScan WalkAway can also be used to determine a preliminary MIC, which may be confirmed using the method described below.

Frozen stock cultures may be used as the initial source of organisms for performing microbroth dilution minimum inhibition concentration (MIC) testing. Stock cultures are passed on their standard growth medium for at least 1 growth cycle (18-24 hours) prior to their use. Most bacteria may be prepared directly from agar plates in 10 mL aliquots of the appropriate broth medium. Bacterial cultures are adjusted to the opacity of a 0.5 McFarland Standard (optical density value of 0.28-0.33 on a Perkin-Elmer Lambda EZ150 Spectrophotometer, Wellesley, Mass., set at a wavelength of 600 nm). The adjusted cultures are then diluted 400 fold (0.25 mL inoculum+100 mL broth) in growth media to produce a starting suspension of approximately  $5 \times 10^5$  colony forming units (CFU)/mL. Most bacterial strains may be tested in cation adjusted Mueller Hinton Broth (CAMHB).

Test compounds ("drugs") are solubilized in a solvent suitable for the assay, such as DMSO. Drug stock solutions may be prepared on the day of testing. Microbroth dilution stock plates may be prepared in two dilution series, 64 to 0.06  $\mu\text{g}$  drug/mL and 0.25 to 0.00025  $\mu\text{g}$  drug/mL. For the high concentration series, 200  $\mu\text{L}$  of stock solution (2 mg/mL) is added to duplicate rows of a 96-well microtiter plate. This is used as the first well in the dilution series. Serial two-fold decremental dilutions are made using a BioMek FX robot (Beckman Coulter Inc., Fullerton, Calif.) with 10 of the remaining 11 wells, each of which will contain 100  $\mu\text{L}$  of the appropriate solvent/diluent. Row 12 contains solvent/diluent only and serves as the control. For the first well of the low concentration series, 200  $\mu\text{L}$  of an 8  $\mu\text{g}$ /mL stock are added to duplicate rows of a 96-well plate. Serial two-fold dilutions are made as described above.

Daughter 96-well plates may be spotted (3.2  $\mu\text{L}$ /well) from the stock plates listed above using the BioMek FX robot and used immediately or frozen at  $-70^{\circ}\text{C}$ . until use. Aerobic organisms are inoculated (100  $\mu\text{L}$  volumes) into the thawed plates using the BioMek FX robot. The inoculated plates are placed in stacks and covered with an empty plate. These plates are then incubated for 16 to 24 hours in ambient atmosphere according to CLSI guidelines (National Committee for Clinical Laboratory Standards, Methods for Dilution, Antimicrobial Tests for Bacteria that Grow Aerobically; Approved Standard-Sixth Edition. NCCLS document M7-A6 [ISBN 1-56238-486-4]).

After inoculation and incubation, the degree of bacterial growth can be estimated visually with the aid of a Test Reading Mirror (Dynex Technologies 220 16) in a darkened room with a single light shining directly through the top of the microbroth tray. The MIC is the lowest concentration of drug that prevents macroscopically visible growth under the conditions of the test.

Additionally, any one or more of the pyrazolyl guanidine compounds described herein can be used to treat a  $\text{F}_1\text{F}_0$ -ATP hydrolase associated disorder (e.g., myocardial infarction, ventricular hypertrophy, coronary artery disease, non-Q wave MI, congestive heart failure, cardiac arrhythmias, unstable angina, chronic stable angina, Prinzmetal's angina, high blood pressure, intermittent claudication, peripheral occlusive arterial disease, thrombotic or thromboembolic symptoms of thromboembolic stroke, venous thrombosis, arterial thrombosis, cerebral thrombosis, pulmonary embolism, cerebral embolism, thrombophilia, disseminated intravascular coagulation, restenosis, atrial fibrillation, ventricular enlargement, atherosclerotic vascular disease, atherosclerotic plaque rupture, atherosclerotic plaque formation, transplant atherosclerosis, vascular remodeling atherosclerosis, cancer, surgery, inflammation, systematic infection, artificial surfaces, interventional cardiology, immobility, medication, pregnancy and fetal loss, and diabetic complications comprising retinopathy, nephropathy and neuropathy) in a subject.

Combination Therapy

Additionally, the guanidine compounds described herein can be used in combination with at least one other therapeutic agent, such as Bz-423 (a benzodiazepine compound as described in U.S. Pat. Nos. 7,144,880 and 7,125,866, U.S. patent application Ser. Nos. 11/586,097, 11/585,492, 11/445,010, 11/324,419, 11/176,719, 11/110,228, 10/935,333, 10/886,450, 10/795,535, 10/634,114, 10/427, 211, 10/217,878, and 09/767,283, and U.S. Provisional Patent Nos. 60/878,519, 60/812,270, 60/802,394, 60/732,045, 60/730,711, 60/704,102, 60/686,348, 60/641,040, 60/607,599, and 60/565,788), potassium channel openers, calcium channel blockers, sodium hydrogen exchanger inhibitors, antiarrhyth-

mic agents, antiatherosclerotic agents, anticoagulants, anti-thrombotic agents, prothrombolytic agents, fibrinogen antagonists, diuretics, antihypertensive agents, ATPase inhibitors, mineralocorticoid receptor antagonists, phosphodiesterase inhibitors, antidiabetic agents, anti-inflammatory agents, antioxidants, angiogenesis modulators, antio-  
teoporosis agents, hormone replacement therapies, hormone  
receptor modulators, oral contraceptives, antiobesity agents,  
antidepressants, antianxiety agents, antipsychotic agents,  
antiproliferative agents, antitumor agents, antiulcer and gas-  
troesophageal reflux disease agents, growth hormone agents  
and/or growth hormone secretagogues, thyroid mimetics,  
anti-infective agents, antiviral agents, antibacterial agents,  
antifungal agents, cholesterol/lipid lowering agents and lipid  
profile therapies, and agents that mimic ischemic precondition-  
ing and/or myocardial stunning, antiatherosclerotic  
agents, anticoagulants, antithrombotic agents, antihyperten-  
sive agents, antidiabetic agents, and antihypertensive agents  
selected from ACE inhibitors, AT-1 receptor antagonists, ET  
receptor antagonists, dual ET/AII receptor antagonists, vaso-  
pepsidase inhibitors, an antiplatelet agent selected from  
GPIIb/IIIa blockers, P2Y<sub>1</sub> and P2Y<sub>12</sub> antagonists, thrombox-  
ane receptor antagonists, or aspirin, along with a pharmaceu-  
tically-acceptable carrier or diluent in a pharmaceutical com-  
position.

#### IV. Pharmaceutical Compositions, Formulations, and Exemplary Administration Routes and Dosing Considerations

Exemplary embodiments of various contemplated medica-  
ments and pharmaceutical compositions are provided below.

##### A. Preparing Medicaments

Compounds of the present invention are useful in the  
preparation of medicaments to treat a variety of conditions,  
such as conditions associated with dysregulation of cell  
death, aberrant cell growth and hyperproliferation. One of  
skill in the art will appreciate that any one or more of the  
compounds described herein, including the many specific  
embodiments, are prepared by applying standard pharmaceu-  
tical manufacturing procedures. Such medicaments can be  
delivered to the subject by using delivery methods that are  
well-known in the pharmaceutical arts.

##### B. Exemplary Pharmaceutical Compositions and Formulation

In some embodiments of the present invention, the com-  
positions are administered alone, while in some other  
embodiments, the compositions are preferably present in a  
pharmaceutical formulation comprising at least one active  
ingredient/agent, as discussed above, together with a solid  
support or alternatively, together with one or more pharma-  
ceutically acceptable carriers and optionally other therapeutic  
agents (e.g., those described in section III hereinabove). Each  
carrier should be "acceptable" in the sense that it is compat-  
ible with the other ingredients of the formulation and not  
injurious to the subject.

Contemplated formulations include those suitable for oral,  
rectal, nasal, topical (including transdermal, buccal and sub-  
lingual), vaginal, parenteral (including subcutaneous, intra-  
muscular, intravenous and intradermal) and pulmonary  
administration. In some embodiments, formulations are con-  
veniently presented in unit dosage form and are prepared by  
any method known in the art of pharmacy. Such methods  
include the step of bringing into association the active ingre-  
dient with the carrier which constitutes one or more accessory  
ingredients. In general, the formulations are prepared by uni-  
formly and intimately bringing into association (e.g., mixing)  
the active ingredient with liquid carriers or finely divided  
solid carriers or both, and then if necessary shaping the prod-  
uct.

Formulations of the present invention suitable for oral  
administration may be presented as discrete units such as  
capsules, cachets or tablets, wherein each preferably contains  
a predetermined amount of the active ingredient; as a powder  
or granules; as a solution or suspension in an aqueous or  
non-aqueous liquid; or as an oil-in-water liquid emulsion or a  
water-in-oil liquid emulsion. In other embodiments, the  
active ingredient is presented as a bolus, electuary, or paste,  
etc.

In some embodiments, tablets comprise at least one active  
ingredient and optionally one or more accessory agents/car-  
riers are made by compressing or molding the respective  
agents. In some embodiments, compressed tablets are pre-  
pared by compressing in a suitable machine the active ingre-  
dient in a free-flowing form such as a powder or granules,  
optionally mixed with a binder (e.g., povidone, gelatin,  
hydroxypropylmethyl cellulose), lubricant, inert diluent, pre-  
servative, disintegrant (e.g., sodium starch glycolate, cross-  
linked povidone, cross-linked sodium carboxymethyl cellu-  
lose) surface-active or dispersing agent. Molded tablets are  
made by molding in a suitable machine a mixture of the  
powdered compound (e.g., active ingredient) moistened with  
an inert liquid diluent. Tablets may optionally be coated or  
scored and may be formulated so as to provide slow or con-  
trolled release of the active ingredient therein using, for  
example, hydroxypropylmethyl cellulose in varying propor-  
tions to provide the desired release profile. Tablets may  
optionally be provided with an enteric coating, to provide  
release in parts of the gut other than the stomach.

Formulations suitable for topical administration in the  
mouth include lozenges comprising the active ingredient in a  
flavored basis, usually sucrose and acacia or tragacanth; pas-  
tilles comprising the active ingredient in an inert basis such as  
gelatin and glycerin, or sucrose and acacia; and mouthwashes  
comprising the active ingredient in a suitable liquid carrier.

Pharmaceutical compositions for topical administration  
according to the present invention are optionally formulated  
as ointments, creams, suspensions, lotions, powders, solu-  
tions, pastes, gels, sprays, aerosols or oils. In alternative  
embodiments, topical formulations comprise patches or  
dressings such as a bandage or adhesive plasters impregnated  
with active ingredient(s), and optionally one or more excipi-  
ents or diluents. In some embodiments, the topical formula-  
tions include a compound(s) that enhances absorption or pen-  
etration of the active agent(s) through the skin or other  
affected areas. Examples of such dermal penetration enhanc-  
ers include dimethylsulfoxide (DMSO) and related ana-  
logues.

If desired, the aqueous phase of a cream base includes, for  
example, at least about 30% w/w of a polyhydric alcohol, i.e.,  
an alcohol having two or more hydroxyl groups such as  
propylene glycol, butane-1,3-diol, mannitol, sorbitol, glyce-  
rol and polyethylene glycol and mixtures thereof.

In some embodiments, oily phase emulsions of this inven-  
tion are constituted from known ingredients in a known man-  
ner. This phase typically comprises a lone emulsifier (other-  
wise known as an emulgent), it is also desirable in some  
embodiments for this phase to further comprise a mixture of  
at least one emulsifier with a fat or an oil or with both a fat and  
an oil.

Preferably, a hydrophilic emulsifier is included together  
with a lipophilic emulsifier so as to act as a stabilizer. In some  
embodiments it is also preferable to include both an oil and a  
fat. Together, the emulsifier(s) with or without stabilizer(s)  
make up the so-called emulsifying wax, and the wax together

with the oil and/or fat make up the so-called emulsifying ointment base which forms the oily dispersed phase of the cream formulations.

Emulgents and emulsion stabilizers suitable for use in the formulation of the present invention include Tween 60, Span 80, cetostearyl alcohol, myristyl alcohol, glyceryl monostearate and sodium lauryl sulfate.

The choice of suitable oils or fats for the formulation is based on achieving the desired properties (e.g., cosmetic properties), since the solubility of the active compound/agent in most oils likely to be used in pharmaceutical emulsion formulations is very low. Thus creams should preferably be non-greasy, non-staining and washable products with suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as di-isoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters known as Crodamol CAP may be used, the last three being preferred esters. These may be used alone or in combination depending on the properties required. Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils can be used.

Formulations suitable for topical administration to the eye also include eye drops wherein the active ingredient is dissolved or suspended in a suitable carrier, especially an aqueous solvent for the agent.

Formulations for rectal administration may be presented as a suppository with suitable base comprising, for example, cocoa butter or a salicylate.

Formulations suitable for vaginal administration may be presented as pessaries, creams, gels, pastes, foams or spray formulations containing in addition to the agent, such carriers as are known in the art to be appropriate.

Formulations suitable for nasal administration, wherein the carrier is a solid, include coarse powders having a particle size, for example, in the range of about 20 to about 500 microns which are administered in the manner in which snuff is taken, i.e., by rapid inhalation (e.g., forced) through the nasal passage from a container of the powder held close up to the nose. Other suitable formulations wherein the carrier is a liquid for administration include, but are not limited to, nasal sprays, drops, or aerosols by nebulizer, and include aqueous or oily solutions of the agents.

Formulations suitable for parenteral administration include aqueous and non-aqueous isotonic sterile injection solutions which may contain antioxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents, and liposomes or other micro-particulate systems which are designed to target the compound to blood components or one or more organs. In some embodiments, the formulations are presented/formulated in unit-dose or multi-dose sealed containers, for example, ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

Preferred unit dosage formulations are those containing a daily dose or unit, daily subdose, as herein above-recited, or an appropriate fraction thereof, of an agent.

It should be understood that in addition to the ingredients particularly mentioned above, the formulations of this inven-

tion may include other agents conventional in the art having regard to the type of formulation in question, for example, those suitable for oral administration may include such further agents as sweeteners, thickeners and flavoring agents. It also is intended that the agents, compositions and methods of this invention be combined with other suitable compositions and therapies. Still other formulations optionally include food additives (suitable sweeteners, flavorings, colorings, etc.), phytonutrients (e.g., flax seed oil), minerals (e.g., Ca, Fe, K, etc.), vitamins, and other acceptable compositions (e.g., conjugated linoelic acid), extenders, and stabilizers, etc.

#### C. Exemplary Administration Routes and Dosing Considerations

Various delivery systems are known and can be used to administer therapeutic agents (e.g., exemplary compounds as described above) of the present invention, e.g., encapsulation in liposomes, microparticles, microcapsules, receptor-mediated endocytosis, and the like. Methods of delivery include, but are not limited to, intra-arterial, intra-muscular, intravenous, intranasal, and oral routes. In specific embodiments, it may be desirable to administer the pharmaceutical compositions of the invention locally to the area in need of treatment; this may be achieved by, for example, and not by way of limitation, local infusion during surgery, injection, or by means of a catheter.

The agents identified can be administered to subjects or individuals susceptible to or at risk of developing pathological growth of target cells and correlated conditions. When the agent is administered to a subject such as a mouse, a rat or a human patient, the agent can be added to a pharmaceutically acceptable carrier and systemically or topically administered to the subject. To identify patients that can be beneficially treated, a tissue sample is removed from the patient and the cells are assayed for sensitivity to the agent.

Therapeutic amounts are empirically determined and vary with the pathology being treated, the subject being treated and the efficacy and toxicity of the agent. When delivered to an animal, the method is useful to further confirm efficacy of the agent. One example of an animal model is MLR/MpJ-lpr/lpr ("MLR-lpr") (available from Jackson Laboratories, Bar Harbor, Me.). MLR-lpr mice develop systemic autoimmune disease. Alternatively, other animal models can be developed by inducing tumor growth, for example, by subcutaneously inoculating nude mice with about  $10^5$  to about  $10^9$  hyperproliferative, cancer or target cells as defined herein. When the tumor is established, the compounds described herein are administered, for example, by subcutaneous injection around the tumor. Tumor measurements to determine reduction of tumor size are made in two dimensions using venier calipers twice a week. Other animal models may also be employed as appropriate. Such animal models for the above-described diseases and conditions are well-known in the art.

In some embodiments, in vivo administration is effected in one dose, continuously or intermittently throughout the course of treatment. Methods of determining the most effective means and dosage of administration are well known to those of skill in the art and vary with the composition used for therapy, the purpose of the therapy, the target cell being treated, and the subject being treated. Single or multiple administrations are carried out with the dose level and pattern being selected by the treating physician.

Suitable dosage formulations and methods of administering the agents are readily determined by those of skill in the art. Preferably, the compounds are administered at about 0.01 mg/kg to about 200 mg/kg, more preferably at about 0.1 mg/kg to about 100 mg/kg, even more preferably at about 0.5 mg/kg to about 50 mg/kg. When the compounds described

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herein are co-administered with another agent (e.g., as sensitizing agents), the effective amount may be less than when the agent is used alone.

The pharmaceutical compositions can be administered orally, intranasally, parenterally or by inhalation therapy, and may take the form of tablets, lozenges, granules, capsules, pills, ampoules, suppositories or aerosol form. They may also take the form of suspensions, solutions and emulsions of the active ingredient in aqueous or non-aqueous diluents, syrups, granulates or powders. In addition to an agent of the present invention, the pharmaceutical compositions can also contain other pharmaceutically active compounds or a plurality of compounds of the invention.

More particularly, an agent of the present invention also referred to herein as the active ingredient, may be administered for therapy by any suitable route including, but not limited to, oral, rectal, nasal, topical (including, but not limited to, transdermal, aerosol, buccal and sublingual), vaginal, parental (including, but not limited to, subcutaneous, intramuscular, intravenous and intradermal) and pulmonary. It is also appreciated that the preferred route varies with the condition and age of the recipient, and the disease being treated.

Ideally, the agent should be administered to achieve peak concentrations of the active compound at sites of disease. This may be achieved, for example, by the intravenous injection of the agent, optionally in saline, or by oral administration, for example, as a tablet, capsule or syrup containing the active ingredient.

Desirable blood levels of the agent may be maintained by a continuous infusion to provide a therapeutic amount of the active ingredient within disease tissue. The use of operative combinations is contemplated to provide therapeutic combinations requiring a lower total dosage of each component than may be required when each individual therapeutic compound or drug is used alone, thereby reducing adverse effects.

D. Exemplary Co-Administration Routes and Dosing Considerations

The invention also includes methods involving co-administration of the compounds described herein with one or more additional active agents. Indeed, it is a further aspect of this invention to provide methods for enhancing prior art therapies and/or pharmaceutical compositions by co-administering a compound of this invention. In co-administration procedures, the agents may be administered concurrently or sequentially. In one embodiment, the compounds described herein are administered prior to the other active agent(s). The pharmaceutical formulations and modes of administration may be any of those described above. In addition, the two or more co-administered chemical agents, biological agents or radiation may each be administered using different modes or different formulations.

The agent or agents to be co-administered depend on the type of condition being treated. For example, when the condition being treated is cancer, the additional agent can be a chemotherapeutic agent or radiation. When the condition being treated is an immune disorder, the additional agent can be an immunosuppressant or an anti-inflammatory agent. When the condition being treated is chronic inflammation, the additional agent can be an anti-inflammatory agent. The additional agents to be co-administered, such as anticancer, immunosuppressant, anti-inflammatory, can be any of the well-known agents in the art, including, but not limited to, those that are currently in clinical use. The determination of appropriate type and dosage of radiation treatment is also within the skill in the art or can be determined with relative ease.

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Treatment of the various conditions associated with abnormal apoptosis is generally limited by the following two major factors: (1) the development of drug resistance and (2) the toxicity of known therapeutic agents. In certain cancers, for example, resistance to chemicals and radiation therapy has been shown to be associated with inhibition of apoptosis. Some therapeutic agents have deleterious side effects, including non-specific lymphotoxicity, renal and bone marrow toxicity.

The methods described herein address both these problems. Drug resistance, where increasing dosages are required to achieve therapeutic benefit, is overcome by co-administering the compounds described herein with the known agent. The compounds described herein sensitize target cells to known agents (and vice versa) and, accordingly, less of these agents are needed to achieve a therapeutic benefit.

The sensitizing function of the claimed compounds also addresses the problems associated with toxic effects of known therapeutics. In instances where the known agent is toxic, it is desirable to limit the dosages administered in all cases, and particularly in those cases where drug resistance has increased the requisite dosage. When the claimed compounds are co-administered with the known agent, they reduce the dosage required which, in turn, reduces the deleterious effects.

## EXAMPLES

The invention now being generally described, will be more readily understood by reference to the following examples, which are included merely for purposes of illustration of certain aspects and embodiments of the present invention, and are not intended to limit the invention.

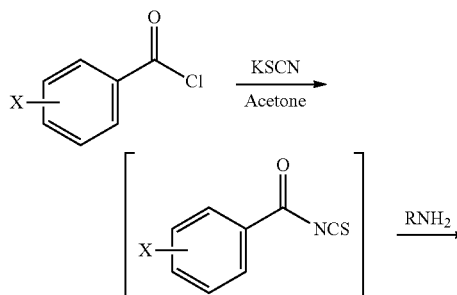
### Example 1

#### Preparation of Pyrazolyl Guanidine Compounds

Described below are exemplary, general synthetic procedures for making pyrazolyl guanidine compounds, along with an exemplary synthetic procedure for making the specific pyrazolyl guanidine compound (Z)-4-chloro-N-(((3,4,5-trifluorobenzyl)amino))((3-(trifluoromethyl)-1H-pyrazol-5-yl)amino)methylene)benzamide.

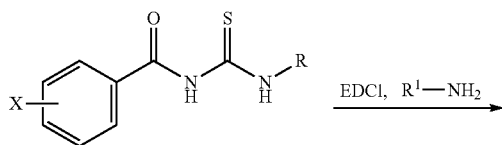
#### Part I: General Method for Making Pyrazolyl Guanidine Compounds

SCHEME 2



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Guanidines can be prepared from an acid chloride, a first amine, and a second amine using a three-step procedure. First, the requisite acid chloride is combined with potassium thiocyanate in an organic solvent, and this mixture is stirred at ambient temperature for 1-4 hours. The resulting mixture is concentrated in vacuo and used immediately.

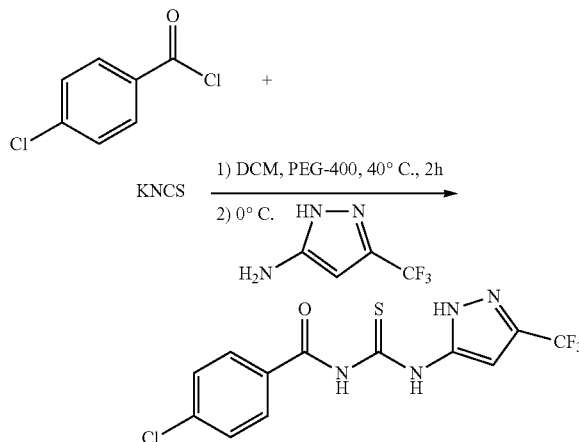
In a second step, an appropriate first amine ( $\text{RNH}_2$ ) is dissolved in an organic solvent, such as methylene chloride, at ambient temperature and the acyl isothiocyanate from the first step is added. The resulting mixture is stirred at ambient temperature for 8-16 hours. The solvents are evaporated in vacuo and the resulting residue treated with a warm non-polar organic solvent, then allowed to cool and collected by filtration. The collected residue is rinsed with a non-polar organic solvent and dried. The resulting residue can be used without further purification. Alternatively, the first amine in the form of a hydrochloride salt is dissolved in an organic solvent and treated with a hindered organic base such as triethylamine then stirred at ambient temperature for 1-4 hours. The acyl isothiocyanate from step 1 is then added and the reaction mixture stirred at ambient temperature for 8-16 hours. The solvents are removed in vacuo and the resulting residue is purified by chromatography.

In the third step, the acyl thiourea from step 2 and an appropriate second amine ( $\text{R}^1\text{—NH}_2$ ) are dissolved in a polar organic solvent such as dimethylformamide at ambient temperature to form a mixture. To this mixture, 1-ethyl-2',2'-dimethylaminopropylcarbodiimide is added and the resulting mixture is stirred until the reaction appears complete by HPLC analysis of aliquots of the reaction mixture. Typical reaction times range from 30 minutes to 12 hours, and the reaction mixture may be heated (e.g., to approximately 60° C.) to accelerate the reaction. Once the reaction appears to be complete by HPLC analysis, the reaction mixture is diluted with an organic solvent (such as ethylacetate), washed with water, washed with brine, and the organic layer is dried over an appropriate drying agent, filtered, and the solvents removed under reduced pressure. The desired product can be purified by chromatography if necessary.

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Part II: Exemplary Synthetic Procedure for Preparing Pyrazolyl Compound (Z)-4-Chloro-N-(((3,4,5-trifluorobenzyl)amino)((3-(trifluoromethyl)-1H-pyrazol-5-yl)amino)methylene)benzamide

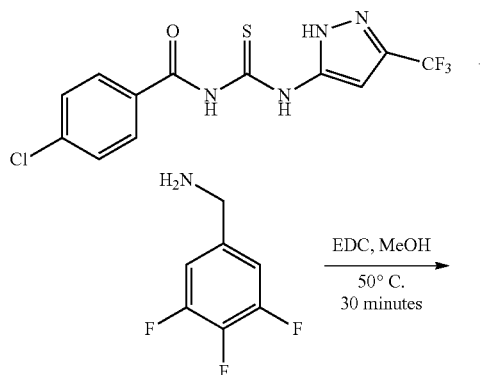
Step A: Representative Procedure for Preparing a Substituted Benzoyl Isothiocyanate in Situ and Conversion to a Thiourea



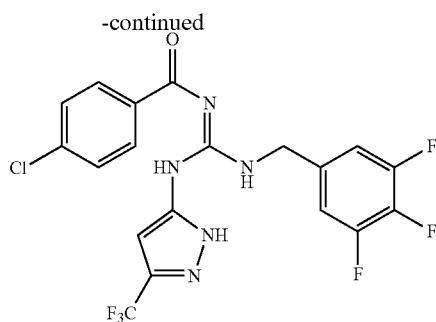
To a suspension of potassium thiocyanate (KNCS) (1.22 g, 12.57 mmol) in dichloromethane (60 mL) was added 400  $\mu\text{L}$  of PEG-400 followed by 4-chlorobenzoyl chloride (2.00 g, 11.43 mmol). The suspension was heated to 40° C. for 2 h, then cooled to room temperature and filtered into an addition funnel. This solution was added dropwise into an ice cold solution of 5-amino-3-trifluoromethylpyrazole (1.73 g, 11.43 mmol) in dichloromethane (60 mL). The reaction was stirred for 20 minutes following the complete addition, and then it was concentrated in vacuo delivering the product as a yellow solid (3.76 g, 94% yield).

$^1\text{H}$ NMR (400 MHz,  $\text{DMSO-d}_6$ )  $\delta$  13.93 (bs, 1H), 12.88 (bs, 1H), 12.00 (bs, 1H), 7.97 (d, 2H,  $J=8.4$  Hz), 7.61 (d, 2H,  $J=8.4$  Hz), 7.16 (bs, 1H).

Step B: Representative Procedure for the Coupling of a Thiourea to an Amine



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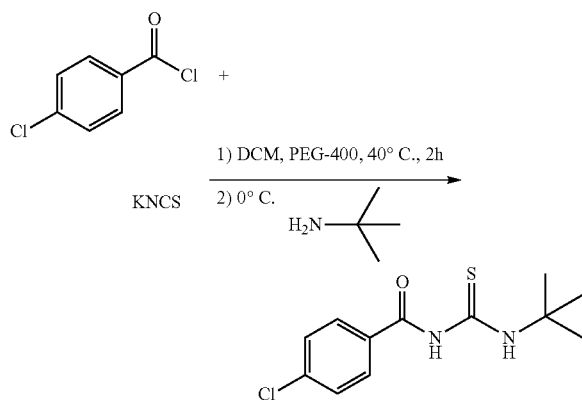


4-Chloro-N-((3-(trifluoromethyl)-1H-pyrazol-5-yl)carbamothioyl)benzamide (500 mg, 1.43 mmol) was dissolved in methanol (5 mL) and 3,4,5-trifluorobenzylamine (462 mg, 2.87 mmol) was added followed by N1-((ethylimino)methylene)-N3,N3-dimethylpropane-1,3-diamine hydrochloride (550 mg, 2.87 mmol). The reaction was stirred at 50° C. for 30 minutes. The crude mixture was then partitioned between water and ethyl acetate. The organic layer was washed with brine, and dried over sodium sulfate, then purified by chromatography (gradient: 95:5 hexanes:EtOAc to 7:3 hexanes:EtOAc). (Z)-4-Chloro-N-(((3,4,5-trifluorobenzyl)amino)((3-(trifluoromethyl)-1H-pyrazol-5-yl)amino)methylene)benzamide was obtained as a solid (221 mg, 32% yield). MS (ES+) 475.8.

## Example 2

Preparation Of (Z)—N-(Tert-butylamino)-(3-(trifluoromethyl)-1H-pyrazol-5-ylamino)methylene)-4-chlorobenzamide

Part I: Exemplary Procedure for Preparation of a Substituted Benzoyl Isothiocyanate In Situ and Conversion to a Thiourea

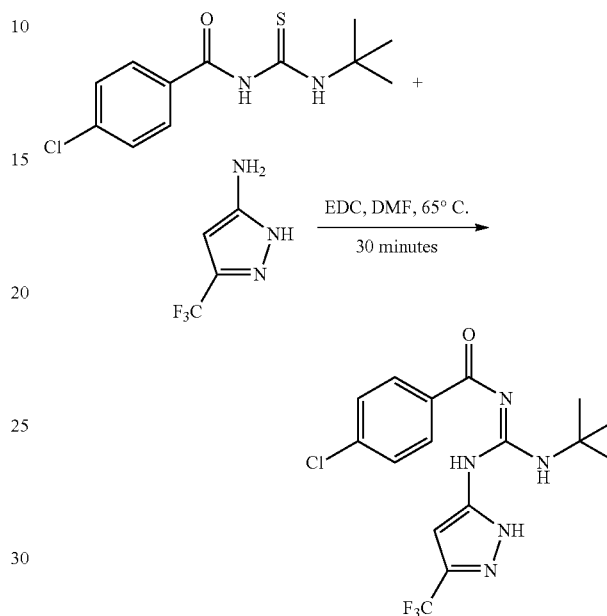


To a suspension of potassium thiocyanate (KNCS) (611 mg, 6.29 mmol) in dichloromethane (30 mL) was added 200  $\mu$ L of PEG-400 followed by 4-chlorobenzoyl chloride (1.00 g, 5.71 mmol). The suspension was heated to 40° C. for 2 h, then cooled to room temperature and filtered into an addition funnel. The solution was added dropwise into an ice cold solution of t-butylamine (418 mg, 5.71 mmol) in dichloromethane (30 mL). The reaction was stirred for 20 minutes following the complete addition, and then it was concentrated in vacuo delivering N-(tert-butylcarbamothioyl)-4-chlo-

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robenzamide as a yellow solid (1.49 g, 96% yield). <sup>1</sup>HNMR (400 MHz, DMSO-d<sub>6</sub>)  $\delta$  11.11 (s, 1H), 11.02 (s, 1H), 7.87 (d, 2H, J=8.8 Hz), 7.54 (d, 2H, J=8.4 Hz), 1.51 (s, 9H).

Part II: Exemplary Procedure for Coupling of a Thiourea to an Amine

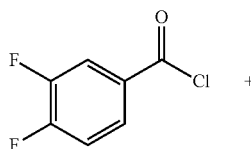


A solution of N-(tert-butylcarbamothioyl)-4-chlorobenzamide (150 mg, 0.55 mmol), 5-amino-3-(trifluoromethyl)pyrazole (92 mg, 0.61 mmol), and N1-((ethylimino)methylene)-N3,N3-dimethylpropane-1,3-diamine hydrochloride (127 mg, 0.67 mmol) in dimethylformamide (5.5 mL) was heated to 65° C. for 30 mins, then allowed to cool to room temperature. The mixture was diluted with EtOAc and washed with water twice, then brine. The organic layer was dried over sodium sulfate and concentrated to provide the title compound in crude form. Purification of the crude by chromatography (gradient: 95:5 hexanes:EtOAc to 70:30 hexanes:EtOAc) provided (Z)—N-((tert-butylamino)(3-(trifluoromethyl)-1H-pyrazol-5-ylamino)methylene)-4-chlorobenzamide as a solid (80 mg, 37% yield). MS (ES+) 387.9.

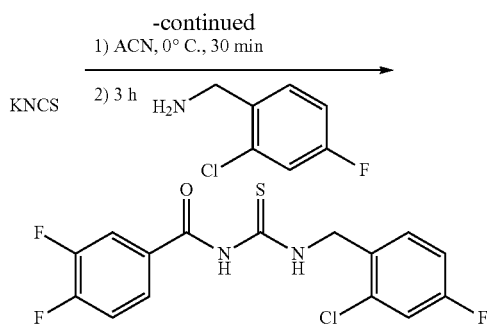
## Example 3

Preparation of (Z)—N-((2-Chloro-4-fluorobenzylamino)(3-(trifluoromethyl)-1H-pyrazol-5-ylamino)methylene)-3,4-difluorobenzamide

Part I: Preparation of N-(2-Chloro-4-fluorobenzylcarbamothioyl)-3,4-difluorobenzamide

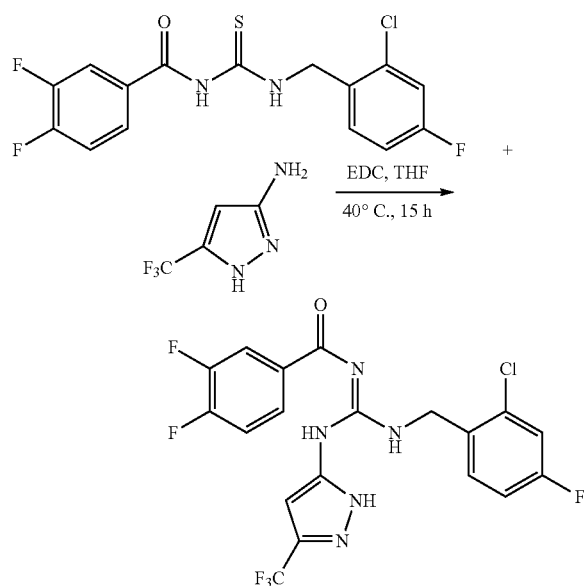


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To a solution of 3,4-difluorobenzoyl chloride (45 mL, 358 mmol) in acetonitrile (1.43 L) was added solid potassium thiocyanate (KNCS) (38.2 g, 393 mmol). The suspension was stirred to 0° C. for 10 min and then the cooling bath was removed. The suspension was stirred at room temperature for an additional 20 min. A solution of 2-chloro-4-fluorobenzylamine (57.1 g, 358 mmol) in acetonitrile (150 mL) was added over 5 minutes. The resulting suspension was stirred at room temperature for 3 hours. The reaction mixture was diluted with water (1.4 L) and stirred for 1 hour. The suspension was filtered, rinsed with water (150 mL) and dried in vacuo at 60° C. to afford N-((2-chloro-4-fluorobenzyl)carbamothioyl)-3,4-difluorobenzamide as a yellow solid (98.3 g, 77% yield). <sup>1</sup>HNMR (400 MHz, DMSO-d<sub>6</sub>) δ 11.56 (bs, 1H), 11.12 (t, 1H, J=5.7 Hz), 8.00 (m, 1H), 7.79 (m, 1H), 7.54 (m, 1H), 7.44 (m, 2H), 7.19 (m, 1H), 4.85 (d, 2H, J=5.7 Hz).

Part II: Preparation of (Z)—N-((2-Chloro-4-fluorobenzylamino)(3-(trifluoromethyl)-1H-pyrazol-5-ylamino)methylene)-3,4-difluorobenzamide



N-((2-Chloro-4-fluorobenzyl)carbamothioyl)-3,4-difluorobenzamide (98.0 g, 273 mmol) and 5-amino-3-trifluoromethylpyrazole (41.3 g, 273 mmol) were dissolved in THF (546 mL). N1-((Ethylimino)methylene)-N3,N3-dimethylpropane-1,3-diamine hydrochloride (57.6 g, 300 mmol) was added and the reaction was stirred at room temperature for 1 h and then heated to 40° C. for 15 h. The crude mixture was

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diluted with water (500 mL) and isopropyl acetate (500 mL). The organic layer was washed with brine (500 mL), dried over sodium sulfate, and concentrated. The residue was diluted with isopropyl acetate (1.3 L) and heated to 65° C. for 1 hour. The solution was allowed to cool to room temperature, filtered and the filtrate was concentrated. The residue was heated to 70° C. in acetonitrile (900 mL) and then allowed to cool to room temperature. The resulting suspension was filtered, rinsed with acetonitrile (200 mL) and dried in vacuo at 60° C. to afford 55 g (43%) of (Z)—N-(((2-chloro-4-fluorobenzyl)amino)(3-(trifluoromethyl)-1H-pyrazol-5-yl)amino)methylene)-3,4-difluorobenzamide as a white solid. <sup>1</sup>HNMR (400 MHz, MeOH-d<sub>4</sub>) δ 7.95 (bs, 2H), 7.50 (t, 1H, J=7.2 Hz), 7.26 (m, 2H), 7.06 (t, 1H, J=7.5 Hz), 6.56 (s, 1H), 4.84 (s, 2H).

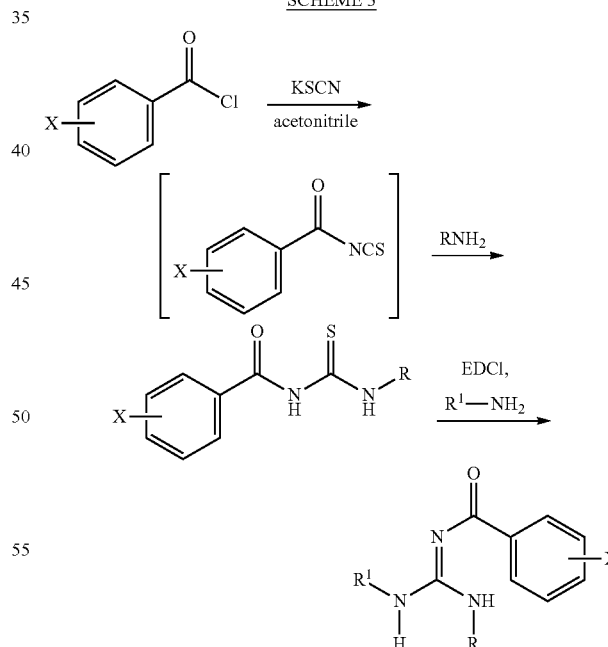
#### Example 4

##### Alternative Procedure for Making Pyrazolyl Guanidine Compounds

Described below is an alternative exemplary general synthetic procedure for making pyrazolyl guanidine compounds, along with an exemplary synthetic procedure for making the specific pyrazolyl guanidine compound N-(((3-(4-(benzyloxy)-2-fluorophenyl)-1H-pyrazol-5-yl)amino)(cyclopentylamino)methylene)-4-(trifluoromethyl)benzamide.

##### Part I: Alternative General Method for Making Pyrazolyl Guanidine Compounds

SCHEME 3



Acyl guanidines can be prepared from an acid chloride, a first amine, and a second amine using a three-step, 2-pot procedure. First, the requisite acid chloride is combined with a slight molar excess of potassium thiocyanate in a polar aprotic solvent (such as acetonitrile) at a temperature in the range of from about 0° C. to room temperature. The resulting mixture is stirred for a time period ranging from 15 minutes to

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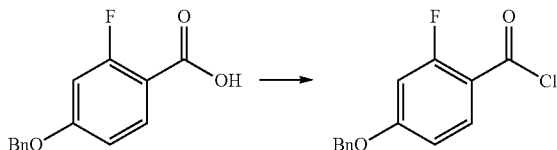
2 hours to provide a reaction mixture containing the acyl isothiocyanate synthetic intermediate compound. This reaction mixture may be used directly in the next reaction or filtered to remove the potassium chloride generated during this first step.

In a second step, the acyl isothiocyanate compound is combined with a second amine (which may be dissolved in a solvent) to provide a reaction mixture that is stirred for a time period ranging from 15 minutes to 2 hours to produce an acyl thiourea product. The acyl thiourea product often precipitates from the reaction mixture and may be collected by filtration. Water may be added to the reaction mixture (typically in amount equal to the volume of organic solvent) to facilitate collection of the acyl thiourea product. The acyl thiourea product is dried in vacuo at approximately ambient temperature.

In a third step, the acyl thiourea product is combined with a coupling agent (such as N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide (EDCI)) and a second amine to produce the acyl guanidine. All starting materials for this reaction may be combined prior to heating the reaction mixture or the EDCI may be added last, once the temperature of the reaction mixture has been raised. Alternatively, the second amine may be added last after combining the thiourea and the EDCI. Once all the starting materials have been combined, the reaction mixture is generally stirred for a time period ranging from about 30 minutes to about 3 hours while the reaction mixture is heated to a temperature ranging from about 45° C. to about 70° C.

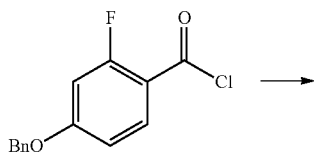
Part II: Exemplary Synthetic Procedure for Preparing  
Pyrazolyl Compound N-(((3-(4-(benzyloxy)-2-fluorophenyl)-1H-pyrazol-5-yl)amino)(cyclopentylamino)methylene)-4-(trifluoromethyl)benzamide

Step A: Preparation of  
4-(Benzyloxy)-2-fluorobenzoyl chloride



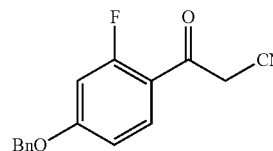
4-Benzyloxy-2-fluoro-benzoic acid (2 g, 8.12 mmol) was suspended in thionyl chloride (5.9 mL) and heated to reflux for 30 minutes. The reaction mixture was then concentrated under reduced pressure, and the resulting residue was dissolved in toluene and re-concentrated twice to remove residual thionyl chloride. This procedure provided the title compound in crude form, which was used in the next reaction without further purification.

Step B: Preparation of 3-(4-(Benzyloxy)-2-fluorophenyl)-3-oxopropanenitrile



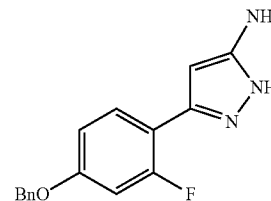
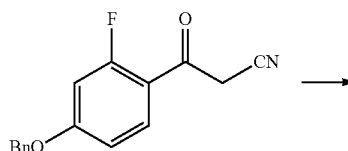
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Acetonitrile (1.66 mL, 31.7 mmol) was dissolved in dry THF (40 mL) and the mixture was cooled to -78 C. Butyllithium (2.5 M, 9.5 mL, 23.8 mmol) was added dropwise, and the resulting reaction mixture was stirred for 15 minutes. A solution of 4-(benzyloxy)-2-fluorobenzoyl chloride (2.1 g, 7.93 mmol) in THF was then added dropwise to the reaction mixture, and the resulting reaction mixture was stirred at -78 C for 40 minutes. Saturated ammonium chloride solution was then added carefully to the reaction mixture, and the resulting mixture was allowed to warm to room temperature. Next, the mixture was partitioned between water and EtOAc, and the organic portion was washed further with brine, then dried over sodium sulfate, and concentrated onto silica gel and purified by chromatography (gradient: 9:1 EtOAc:hexanes to 1:1 EtOAc:hexanes to 100% ethyl acetate) to give the title compound in 79% yield.

Step C: Preparation of 3-(4-(Benzyloxy)-2-fluorophenyl)-1H-pyrazol-5-amine

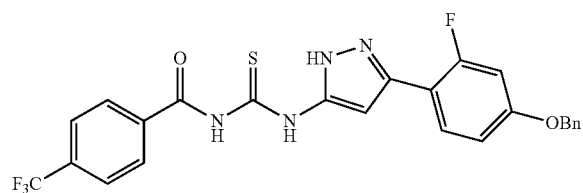
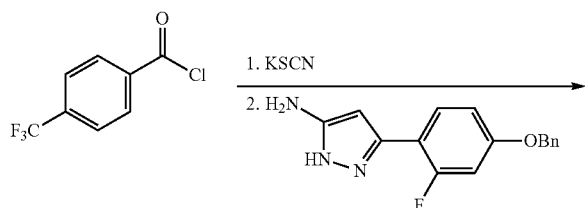


3-(4-(Benzyloxy)-2-fluorophenyl)-3-oxopropanenitrile (1.7 g, 6.3 mmol) was dissolved in ethanol (21 mL), and then hydrazine (0.22 mL, 6.9 mmol) was added. The reaction mixture was stirred at room temperature for about one hour, and the progress of the reaction was followed by thin-layer chromatography. If no progress had been made, the temperature was gradually increased until the reaction began proceeding. As soon as the reaction appeared complete by thin-layer chromatography, the crude material was concentrated in vacuo and purified by chromatography to provide the title compound 97% yield.



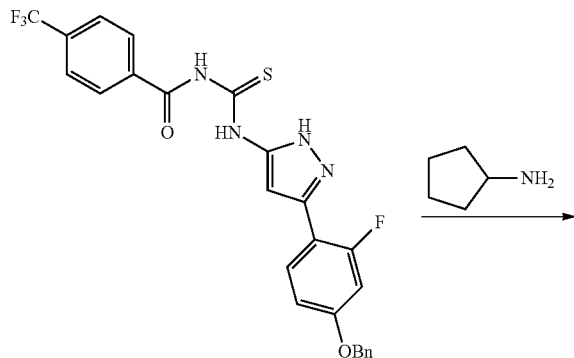
**61**

Step D: Preparation of N-(3-(4-(Benzyloxy)-2-fluorophenyl)-1H-pyrazol-5-ylcarbamothioyl)-4-(trifluoromethyl)benzamide

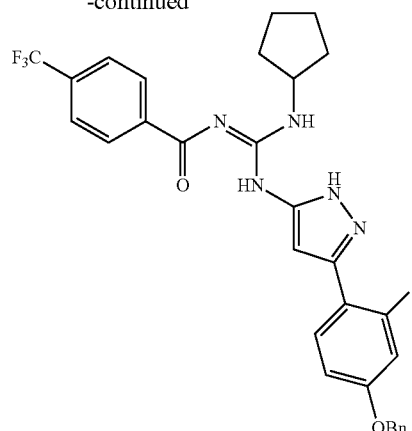


4-Trifluoromethylbenzoyl chloride (590 mg, 2.83 mmol) was dissolved in acetonitrile (~30 mL) and potassium thiocyanate (302 mg, 3.22 mmol) was added to provide a reaction mixture. The reaction mixture was stirred at room temperature for 30 minutes, and then 3-(4-benzyloxy-2-fluorophenyl)-1H-pyrazol-5-amine (801 mg, 2.83 mmol) was added to the reaction mixture. Next, the reaction mixture was stirred at room temperature overnight, then concentrated in vacuo, slurried with water, and collected by filtration. The wet solid was held under heated vacuum for 24 hours to provide the title compound in 81% yield.

Step E: Preparation of N-(((3-(4-(Benzyloxy)-2-fluorophenyl)-1H-pyrazol-5-yl)amino)(cyclopentylamino)methylene)-4-(trifluoromethyl)benzamide

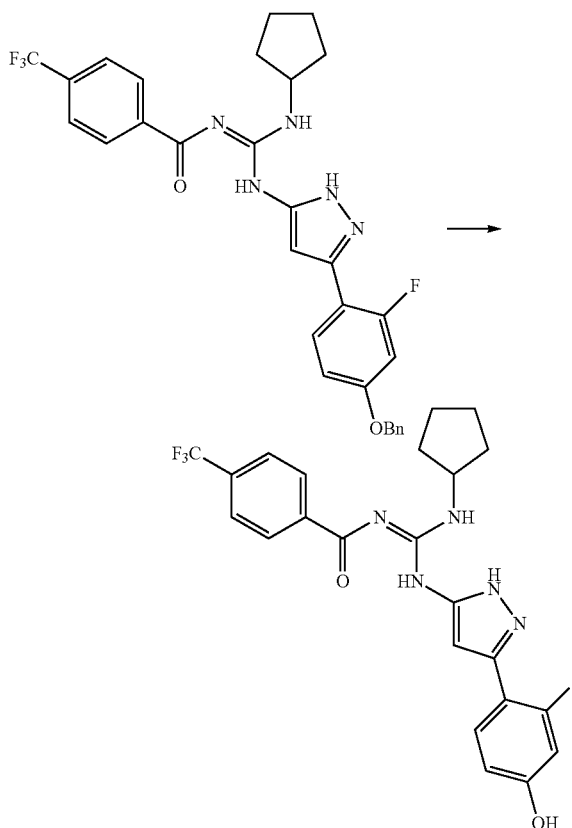
**62**

-continued



N-((3-(4-(Benzyloxy)-2-fluorophenyl)-1H-pyrazol-5-yl)carbamothioyl)-4-(trifluoromethyl)benzamide (154 mg, 0.3 mmol) and EDCI (63 mg, 0.33 mmol) were suspended in THF (4 mL) and cyclopentylamine (0.044 mL, 0.45 mmol) was added. The resulting mixture was stirred at 50° C. for 45 minutes, then concentrated onto silica gel and purified by chromatography (gradient: 9:1 hexanes:EtOAc to 6:4 hexanes:EtOAc) to provide the title compound in 53% yield.

Step F: Preparation of N-(((3-(4-(Benzyloxy)-2-fluorophenyl)-1H-pyrazol-5-yl)amino)(cyclopentylamino)methylene)-4-(trifluoromethyl)benzamide



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N-(((3-(4-(Benzyloxy)-2-fluorophenyl)-1H-pyrazol-5-yl)amino)(cyclopentylamino) methylene)-4-(trifluoromethyl)benzamide (90 mg, 0.16 mmol) was dissolved in methanol (2 mL), and nitrogen gas was bubbled through briefly. 10% Palladium on carbon (84 mg) was then added to the reaction mixture, followed by the addition of ammonium formate (50 mg, 0.8 mmol). The reaction vessel was sealed and then heated to 65° C. for 1 hour. Next, the reaction mixture was cooled, and then filtered through a plug of celite. The filtrate was concentrated onto silica gel, and the product purified by chromatography to give the title compound in 12% yield.

## Example 5

## Pyrazolyl Guanidine Compounds &amp; Characterization Data

Compounds in Table 2 below were prepared based on the procedures described in Examples 1-4 and procedures described in the detailed description. Starting materials can be obtained from commercial sources (e.g., acid chloride: 4-chlorobenzoyl chloride, 3-chlorobenzoyl chloride, and 4-fluorobenzoyl chloride; first amine compound: 2-trifluoromethylaniline, 2-tert-butylaniline, 4-fluoro-2-chlorobenzylamine, cycloheptylamine, tetrahydro-2H-pyran-4-amine; and second amine: 3-(trifluoromethyl)-1H-pyrazol-5-amine, 3-methyl-1H-pyrazol-5-amine, 3-(difluoromethyl)-1H-pyrazol-5-amine) or readily prepared from commercially available materials. Furthermore, exemplary compounds were characterized by high performance liquid chromatography (HPLC), mass spectrometry (MS) and/or <sup>1</sup>H nuclear magnetic resonance spectroscopy. Unless indicated otherwise, mass spectral data in Table 2 was collected using electrospray ionization in the positive ion mode. The symbol “(M-H)<sup>+</sup>” indicates that mass spectral data was collected in the negative

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ion mode. The HPLC method and retention time, along with mass spectral data are provided in Table 2 below. HPLC methods used are as follows: Method A conditions were Waters C-18 column, 4.6×150 mm, 3.5 micron, 23° C., 1.0 mL/min, 1 min 25% MeCN in H<sub>2</sub>O (0.1% TFA), 10 min gradient of 25%-95% MeCN in H<sub>2</sub>O (0.1% TFA), 95% MeCN in H<sub>2</sub>O (0.1% TFA) for 5 min, and then equilibration to 25% MeCN in H<sub>2</sub>O (0.1% TFA) over 2.0 min; Method B conditions were Agilent Zorbax C-18 column, 4.6×50 mm, 1.8 micron, 23° C., 1.0 mL/min, 1 min 25% MeCN in H<sub>2</sub>O (0.1% TFA), 5 min gradient of 25%-95% MeCN in H<sub>2</sub>O (0.1% TFA), 1 min at 95% MeCN in H<sub>2</sub>O (0.1% TFA), and then equilibration to 25% MeCN in H<sub>2</sub>O (0.1% TFA) over 1.0 min; Method C conditions were Phenomenex Kinetex C18 (3.0 mm×50 mm), 2.6 micron, 58° C., 1.5 mL/min, 4 min gradient 5% MeCN (0.1% TFA) in H<sub>2</sub>O (0.1% TFA) to 100% MeCN (0.1% TFA), 100% MeCN (0.1% TFA) for 0.5 min, and then equilibration to 5% MeCN (0.1% TFA) in H<sub>2</sub>O (0.1% TFA) over 1.5 min; Method D conditions were Phenomenex Kinetex C18 (3.0 mm×50 mm), 2.6 micron, 40° C., 1.5 mL/min, 4 min gradient 5% MeCN (0.1% TFA) in H<sub>2</sub>O (0.1% TFA) to 100% MeCN (0.1% TFA), 100% MeCN (0.1% TFA) for 0.5 min, and then equilibration to 5% MeCN (0.1% TFA) in H<sub>2</sub>O (0.1% TFA) over 1.5 min; and Method E conditions were Waters Symmetry C18 (4.6 mm×150 mm), 3.5 micron, 26° C., 2.0 mL/min, 1 min 25% MeCN (0.05% TFA) in H<sub>2</sub>O (0.05% TFA), 7 min gradient of 25%-95% MeCN (0.05% TFA) in H<sub>2</sub>O (0.05% TFA), 95% MeCN (0.05% TFA) in H<sub>2</sub>O (0.05% TFA) for 2 min, and then equilibration to 25% MeCN (0.05% TFA) in H<sub>2</sub>O (0.05% TFA) over 2.0 min. The phrase “MeCN (0.05% TFA)” is art-recognized and refers to acetonitrile containing 0.05% wt/wt trifluoroacetic acid. The symbol “NA” indicates that no data was available.

<sup>1</sup>H nuclear magnetic resonance data for exemplary compounds is provided in Table 3.

TABLE 2

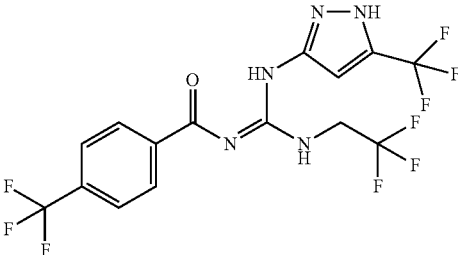
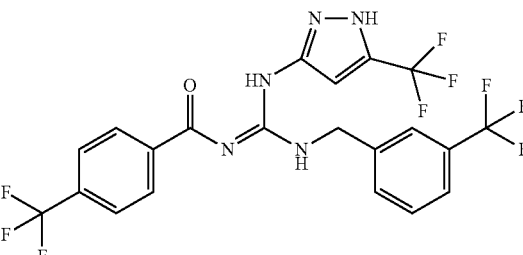
Compound No.	Chemical Structure	Calculated MW (g/mol)	MS (m/z)	HPLC Method	HPLC Retention Time (min)
A-1		447.3	447.9	A	11.27
A-2		523.4	523.9	B	6.98

TABLE 2-continued

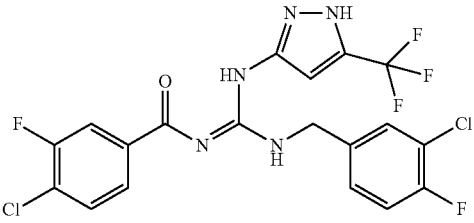
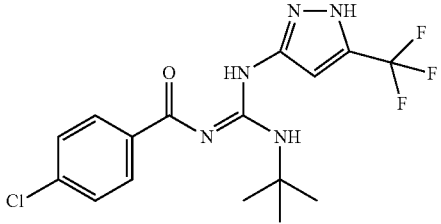
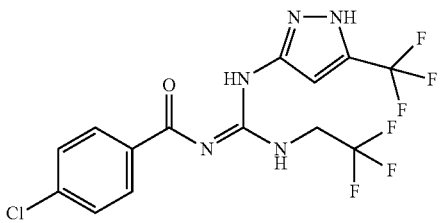
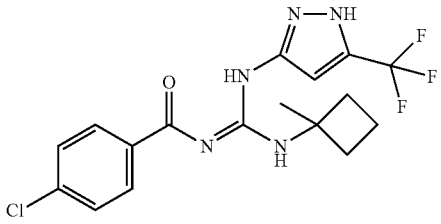
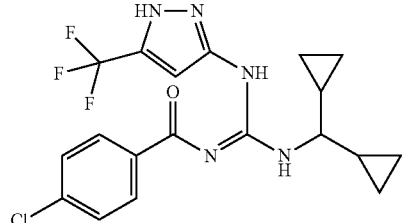
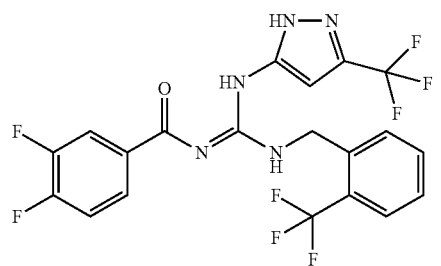
Compound No.	Chemical Structure	Calculated MW (g/mol)	MS (m/z)	HPLC Method	HPLC Retention Time (min)
A-3		492.2	491.7	B	6.96
A-4		387.8	387.9	B	6.59
A-5		413.7	413.8	B	6.33
A-6		399.8	399.9	B	6.17
A-7		425.8	425.9	B	5.85
A-8		491.1	492	C	2.86

TABLE 2-continued

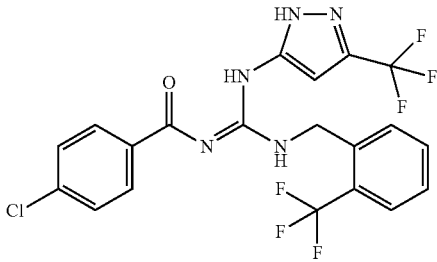
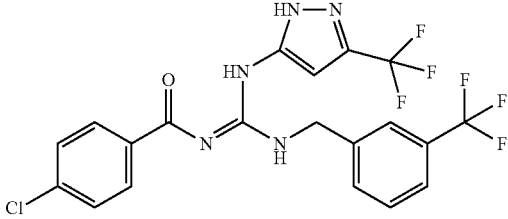
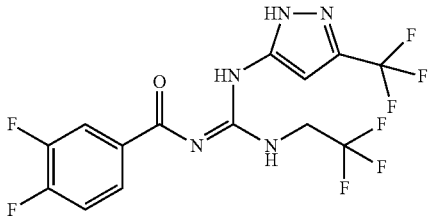
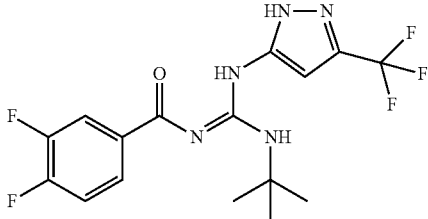
Compound No.	Chemical Structure	Calculated	MS (m/z)	HPLC Method	HPLC Retention
		MW (g/mol)			Time (min)
A-9		489.1	490	C	2.81
A-10		489.1	490	C	2.72
A-11		415.1	416	C	2.65
A-12		389.1	390	C	2.74
A-13		421.3	388	C	2.66

TABLE 2-continued

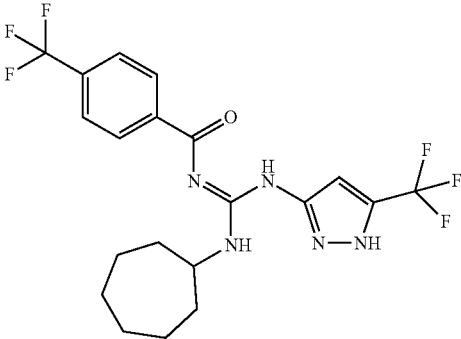
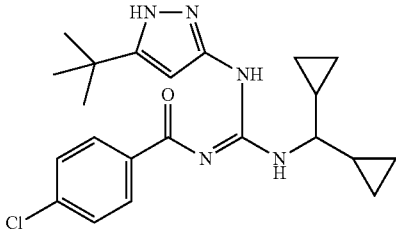
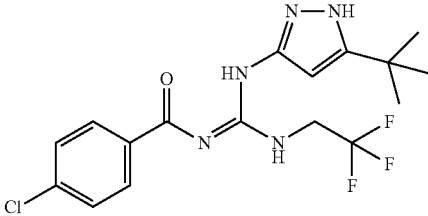
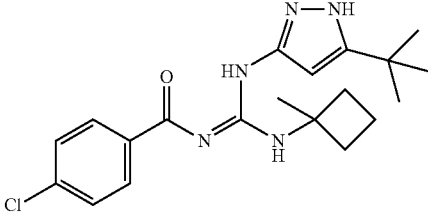
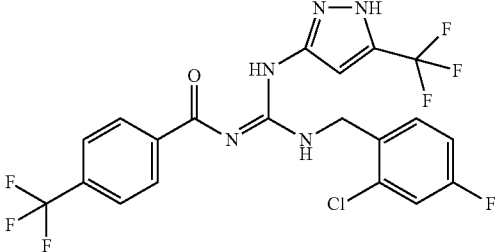
Compound No.	Chemical Structure	Calculated	MS	HPLC	HPLC
		MW (g/mol)	(m/z)	Method	Retention Time (min)
A-14		461.4	461.9	B	6.46
A-15		413.9	413.95, 415.94	A	8.62
A-16		401.8	401.87, 403.87	A	11.14
A-17		387.9	387.94, 389.90	A	8.95
A-18		507.8	508	C	2.75

TABLE 2-continued

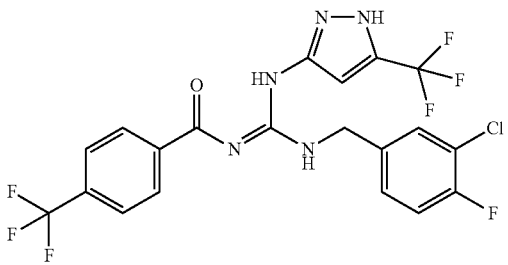
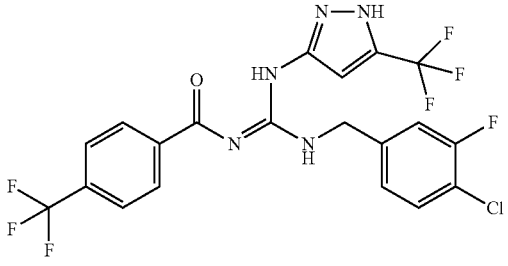
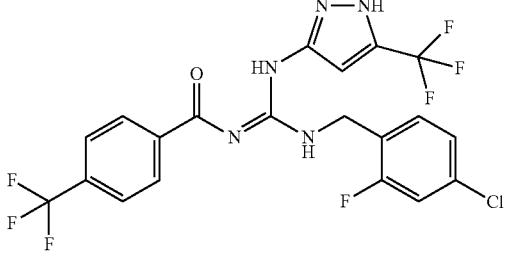
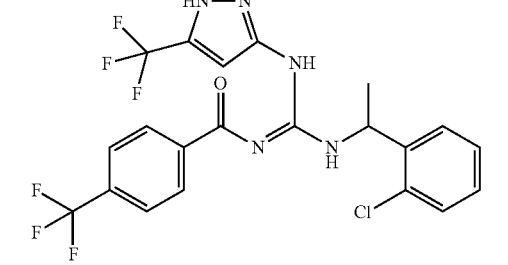
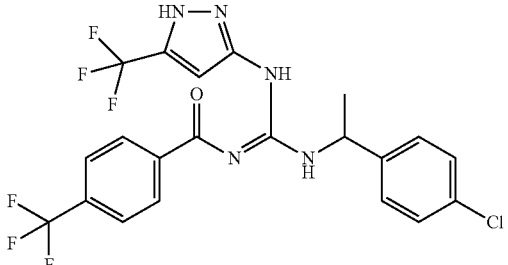
Compound No.	Chemical Structure	Calculated	MS (m/z)	HPLC Method	HPLC Retention
		MW (g/mol)			Time (min)
A-19		507.8	508	C	2.7
A-20		507.8	508	C	2.72
A-21		503.8	508	C	2.77
A-22		503.8	504	C	2.9
A-23		475.8	504	C	2.8

TABLE 2-continued

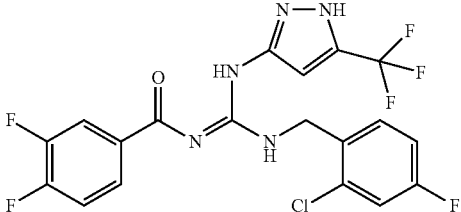
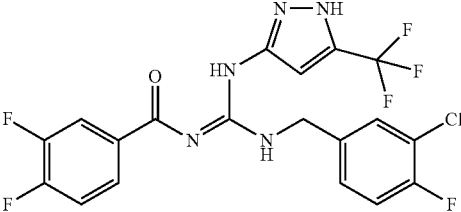
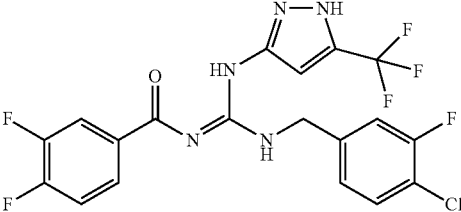
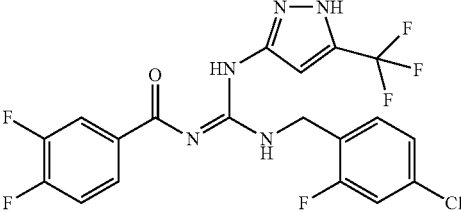
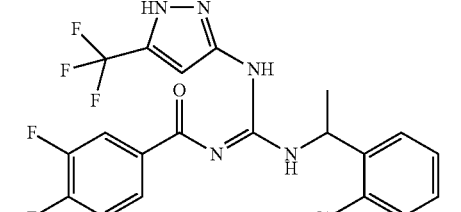
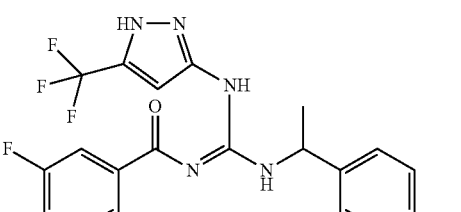
Compound No.	Chemical Structure	Calculated	MS (m/z)	HPLC Method	HPLC Retention
		MW (g/mol)			Time (min)
A-24		475.8	476	C	2.61
A-25		475.8	476	C	2.57
A-26		475.8	476	C	2.59
A-27		475.8	476	C	2.63
A-28		471.8	472	C	2.76
A-29		471.8	472	C	2.67

TABLE 2-continued

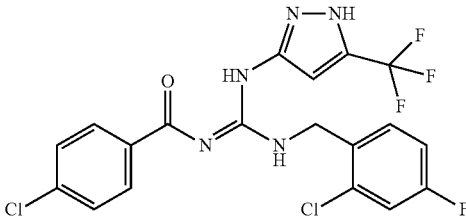
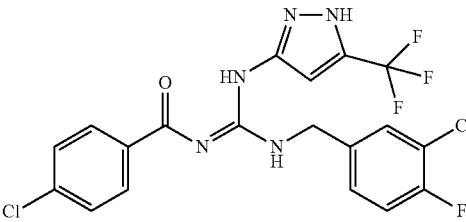
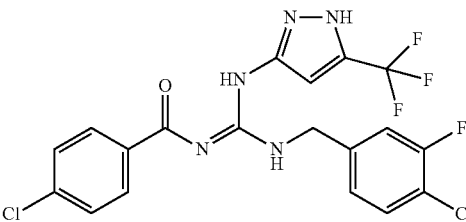
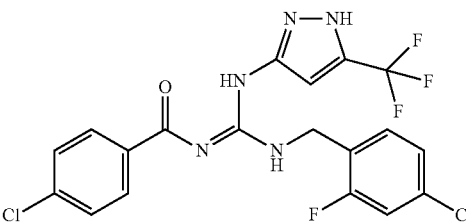
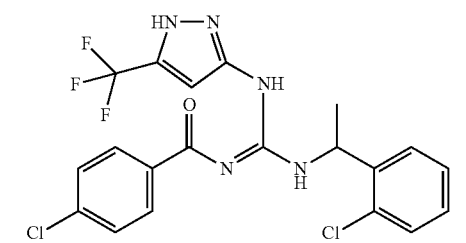
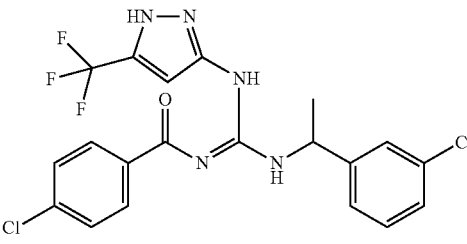
Compound No.	Chemical Structure	Calculated MW (g/mol)	MS (m/z)	HPLC Method	HPLC Retention Time (min)
A-30		474.2	474	C	2.53
A-31		474.2	474	C	2.51
A-32		474.2	474	C	2.53
A-33		474.2	474	C	2.57
A-34		470.3	470	C	2.7
A-35		470.3	470	C	2.62



TABLE 2-continued

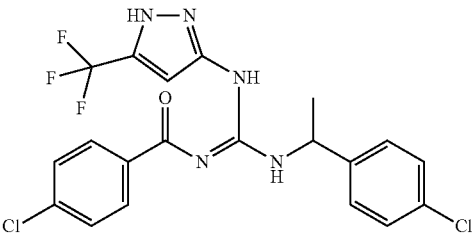
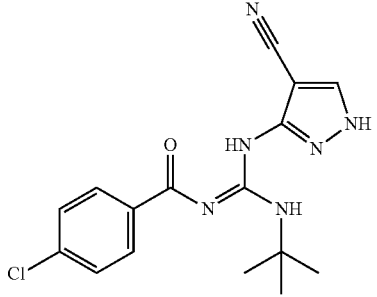
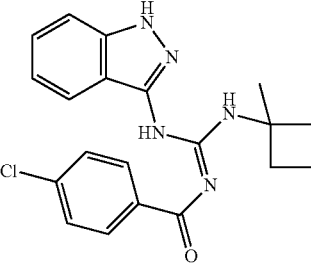
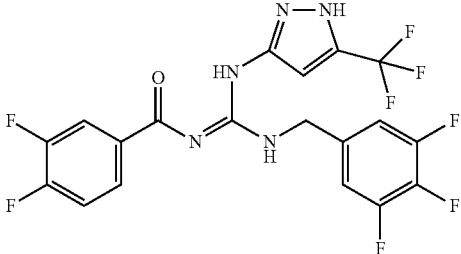
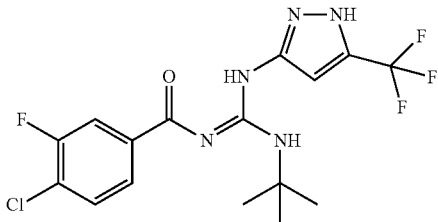
Compound No.	Chemical Structure	Calculated	MS (m/z)	HPLC Method	HPLC Retention
		MW (g/mol)			Time (min)
A-36		470.3	470	C	2.59
A-37		344.8	344.9	B	6.49
A-38		381.9	381.93, 383.89	A	12.59
A-39		477.3	477.8	B	6.53
A-40		405.78	406	B	7.04

TABLE 2-continued

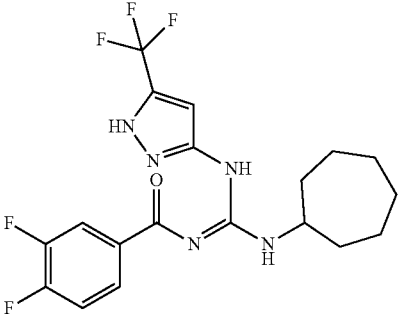
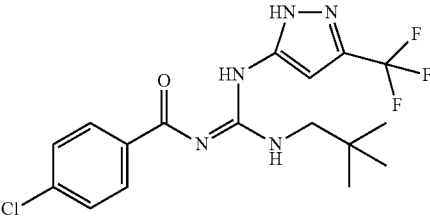
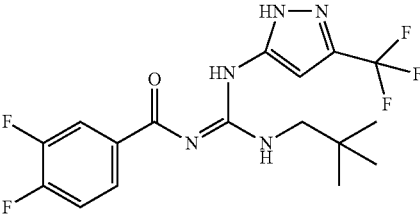
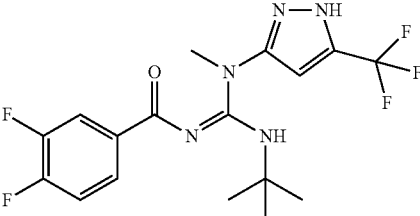
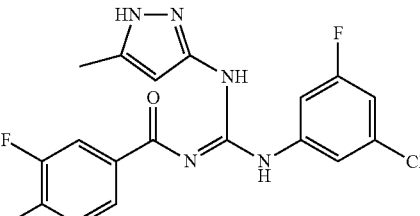
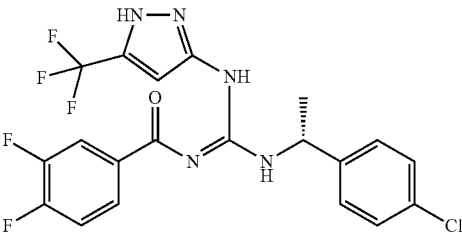
Compound No.	Chemical Structure	Calculated MW (g/mol)	MS (m/z)	HPLC Method	HPLC Retention Time (min)
A-41		429.4	NA	B	6.18
A-42		401.8	338.00, 401.91, 423.85	B	5.46
A-43		403.4	340.02, 403.93, 425.87	B	5.73
A-44		403.4	403.93, 425.87	B	7.58
A-45		407.8	407.79	B	7
A-46		471.8	471.84, 493.78	B	6.82

TABLE 2-continued

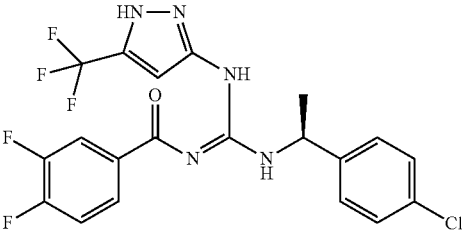
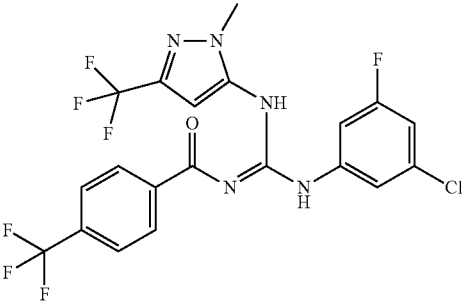
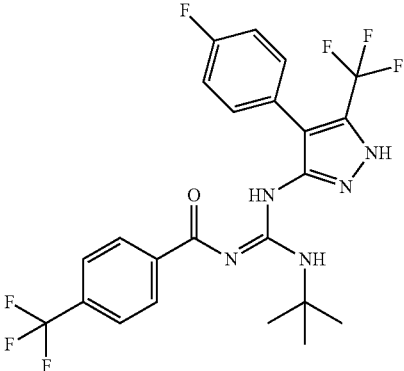
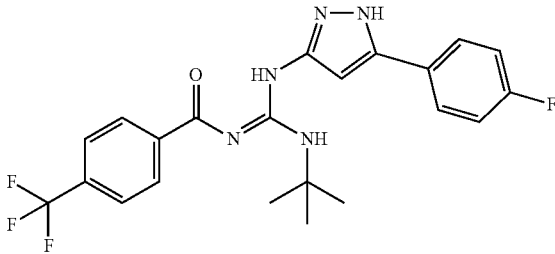
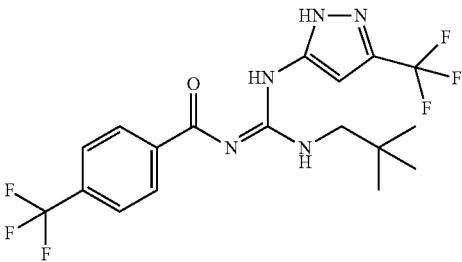
Compound No.	Chemical Structure	Calculated MW (g/mol)	MS (m/z)	HPLC Method	HPLC Retention Time (min)
A-47		471.8	471.78, 493.72	B	6.82
A-48		507.8	507.82	B	7.07
A-49		447.4	447.94	B	6.29
A-50		447.4	447.94	B	6.8
A-51		435.4	372.01, 435.92, 457.86	B	6.02

TABLE 2-continued

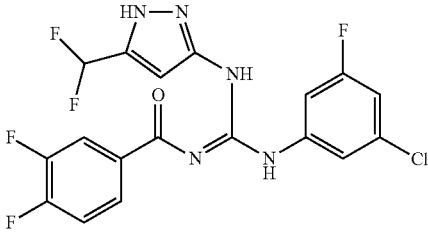
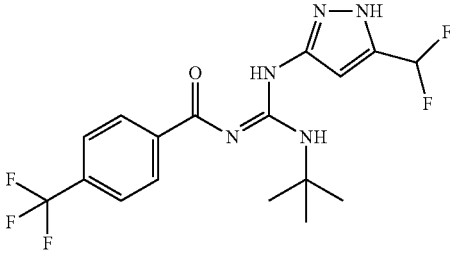
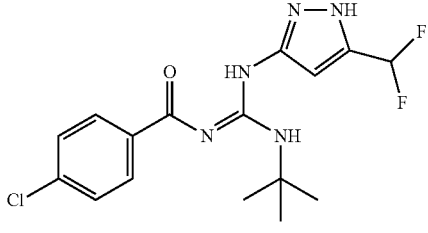
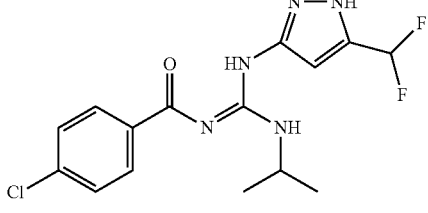
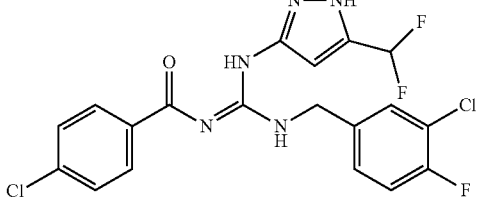
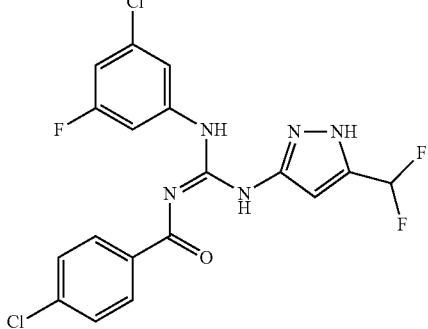
Compound No.	Chemical Structure	Calculated MW (g/mol)	MS (m/z)	HPLC Method	HPLC Retention Time (min)
A-52		443.76	443.76, 445.79	A	12.35
A-53		403.35	403.91	A	11.28
A-54		369.8	369.99, 372.01	A	10.43
A-55		355.77	355.98, 357.97	A	6.91
A-56		456.25	455.89, 457.86	A	9.93
A-57		442.22	441.93, 443.89	A	12.68

TABLE 2-continued

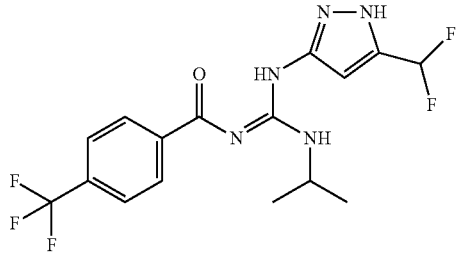
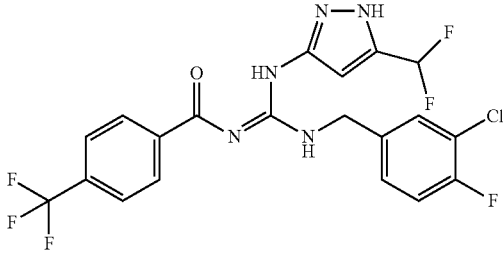
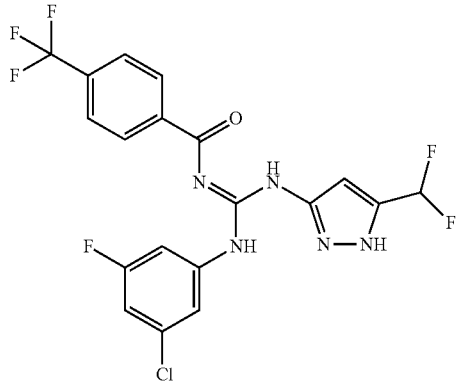
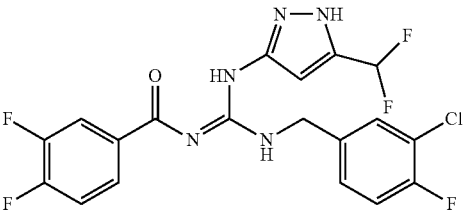
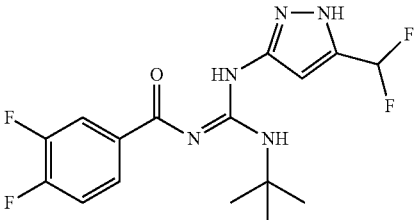
Compound No.	Chemical Structure	Calculated	MS	HPLC	HPLC
		MW (g/mol)	(m/z)	Method	Retention Time (min)
A-58		389.32	389.99	A	7.91
A-59		489.8	489.87, 491.88	A	10.9
A-60		475.77	475.89, 477.85	A	12.67
A-61		457.78	457.93, 459.95	A	10.45
A-62		371.33	372.04	A	10.76

TABLE 2-continued

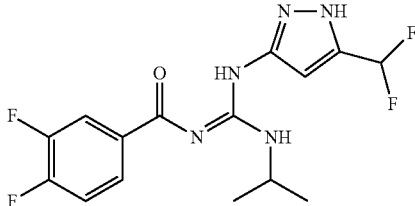
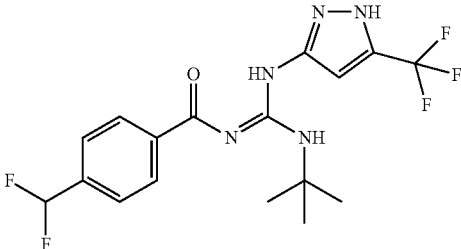
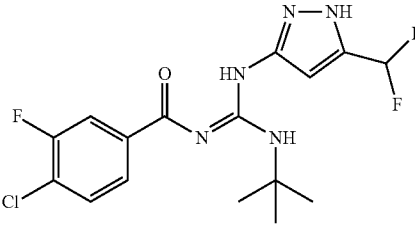
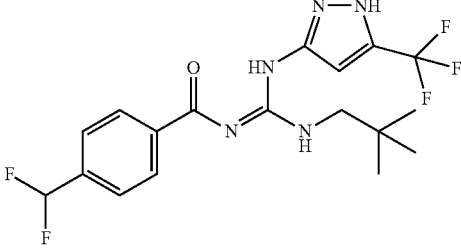
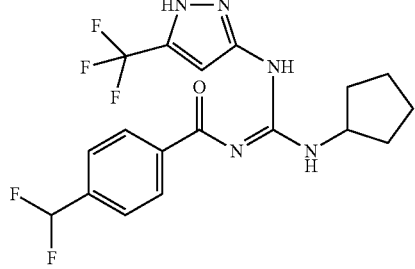
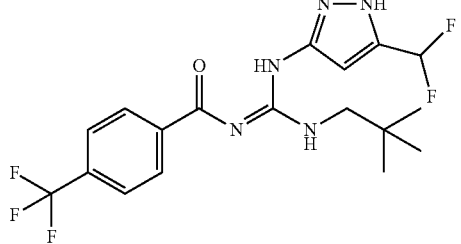
Compound No.	Chemical Structure	Calculated MW (g/mol)	MS (m/z)	HPLC Method	HPLC Retention Time (min)
A-63		357.31	358.03	A	7.26
A-64		403.35	403.9	A	10.6
A-65		387.79	387.83, 389.83	A	11.92
A-66		417.38	417.97	A	8.52
A-67		415.36	415.91	A	8.05
A-68		417.38	NA	NA	NA

TABLE 2-continued

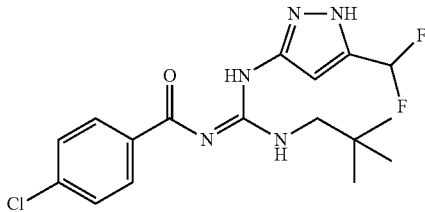
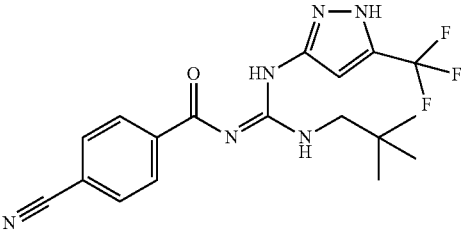
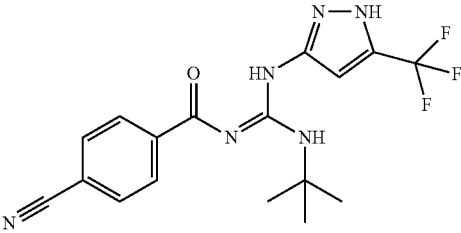
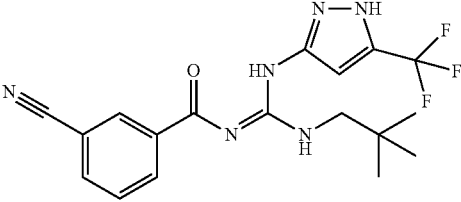
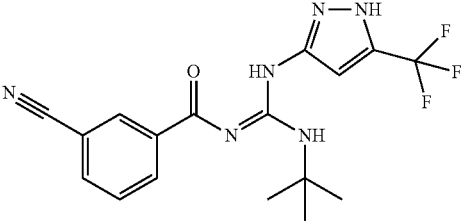
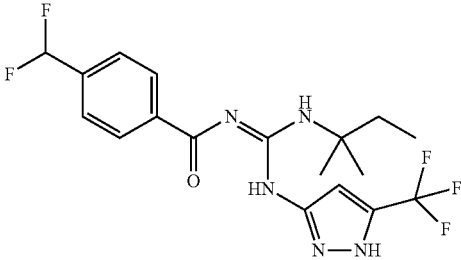
Compound No.	Chemical Structure	Calculated MW (g/mol)	MS (m/z)	HPLC Method	HPLC Retention Time (min)
A-69		383.82	383.92, 385.88	A	7.93
A-70		392.38	392.92	A	9.37
A-71		378.35	378.87	A	10.79
A-72		392.38	392.93	A	9.46
A-73		378.35	378.9	A	10.75
A-74		417.38	417.97	A	11.08

TABLE 2-continued

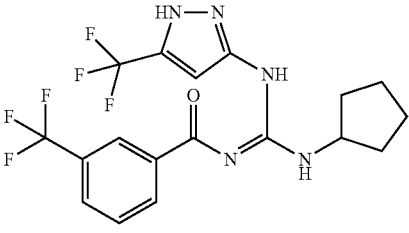
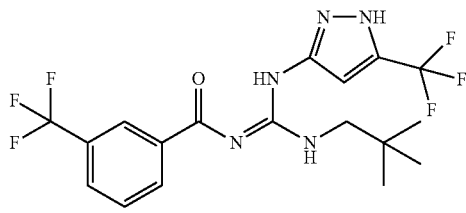
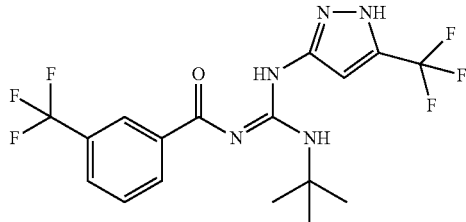
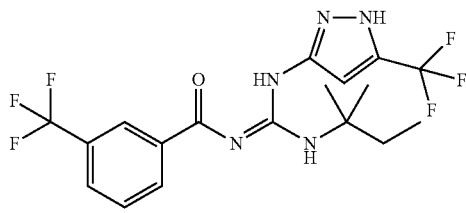
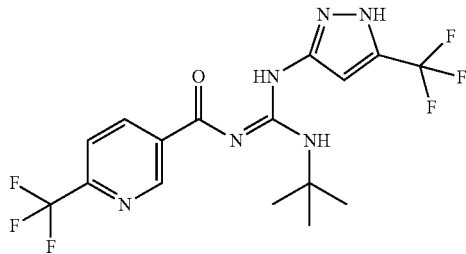
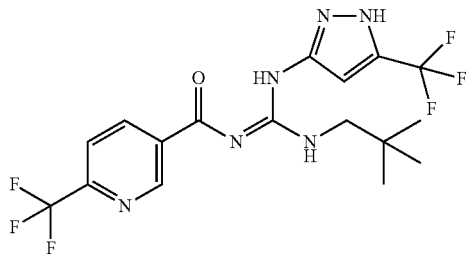
Compound No.	Chemical Structure	Calculated MW (g/mol)	MS (m/z)	HPLC Method	HPLC Retention Time (min)
A-75		433.35	433.91	A	9.79
A-76		435.37	435.92	A	10.42
A-77		421.34	421.94	A	12.15
A-78		435.37	435.97	A	12.58
A-79		422.33	422.89	A	11.57
A-80		436.35	436.9	A	11.19



TABLE 2-continued

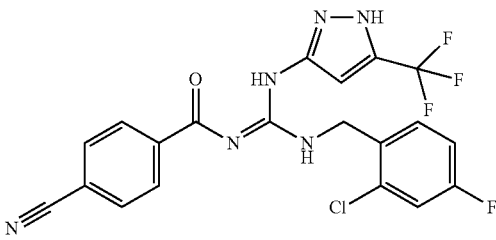
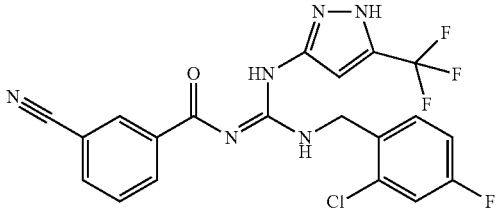
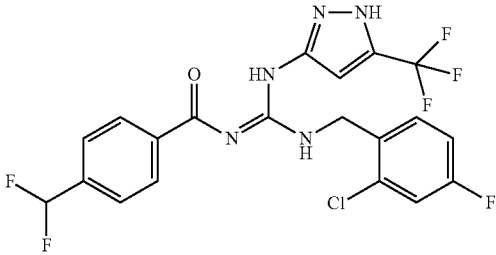
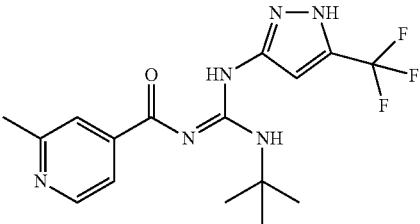
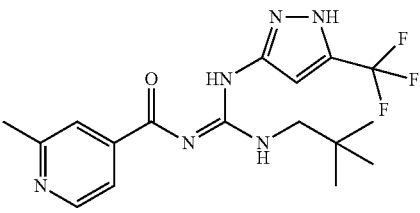
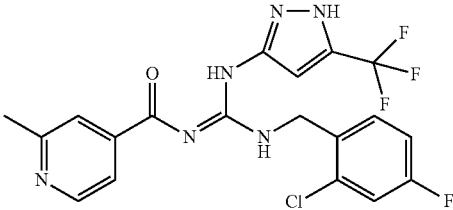
Compound No.	Chemical Structure	Calculated MW (g/mol)	MS (m/z)	HPLC Method	HPLC Retention Time (min)
A-81		464.8	464.88, 466.84	A	10.9
A-82		464.8	464.88, 466.84	A	10.87
A-83		489.8	489.86, 491.82	A	10.58
A-84		368.36	369.03	A	5.9
A-85		382.38	383.03	A	6.12
A-86		454.81	454.87, 456.85	A	6.54

TABLE 2-continued

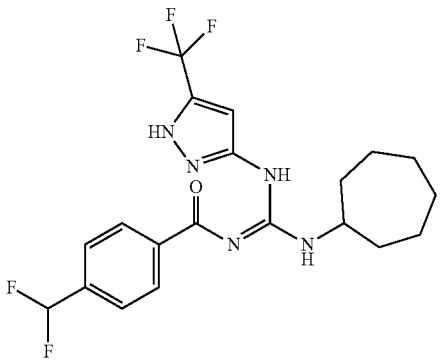
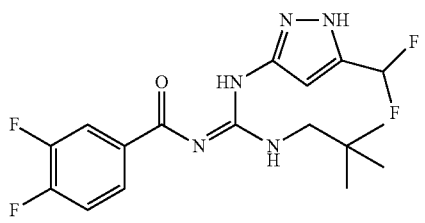
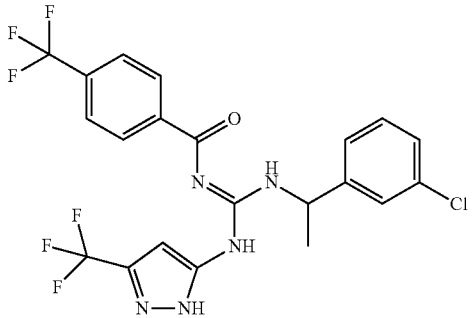
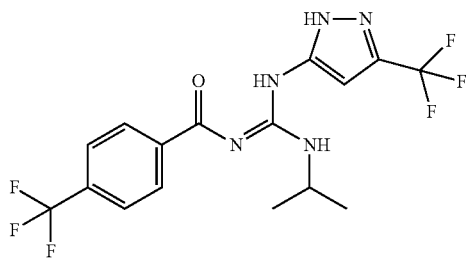
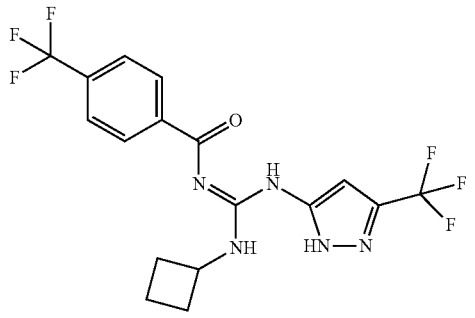
Compound No.	Chemical Structure	Calculated MW (g/mol)	MS (m/z)	HPLC Method	HPLC Retention Time (min)
A-87		443.41	443.94	A	9.11
A-88		385.36	385.97	A	8.42
A-89		503.84	504	C	2.8
A-90		407.32	508	C	2.12
A-91		419.33	420	C	2.28

TABLE 2-continued

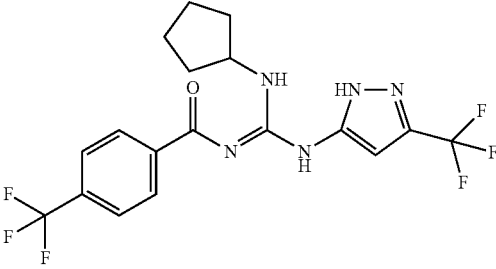
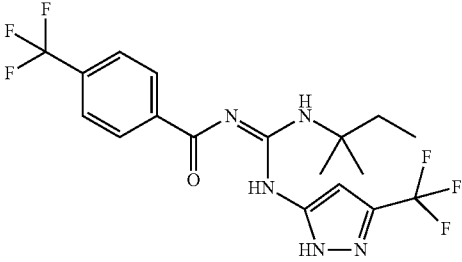
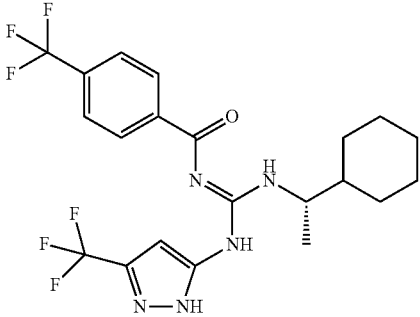
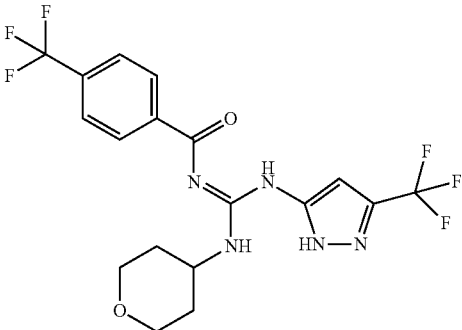
Compound No.	Chemical Structure	Calculated	MS	HPLC	HPLC
		MW (g/mol)	(m/z)	Method	Retention Time (min)
A-92		433.36	434	C	2.28
A-93		435.38	436	C	2.82
A-94		475.44	476	C	2.63
A-95		449.36	450	C	2.09

TABLE 2-continued

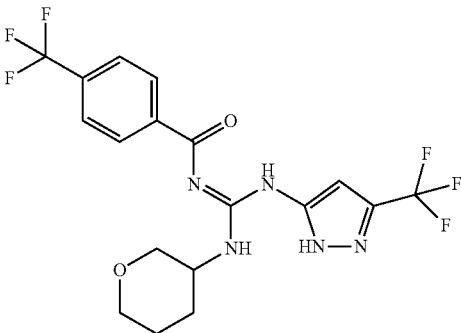
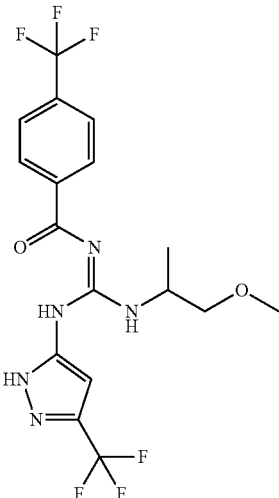
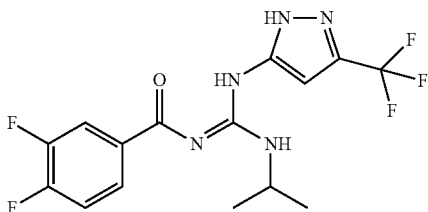
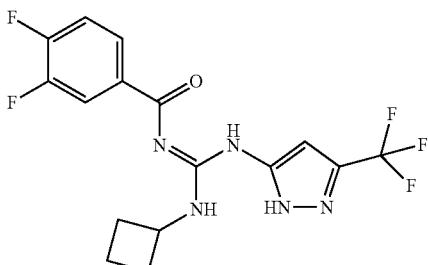
Compound No.	Chemical Structure	Calculated	MS	HPLC Method	HPLC
		MW (g/mol)	(m/z)		Retention Time (min)
A-96		449.36	450	C	2.17
A-97		437.35	438	C	2.13
A-98		375.3	376	C	1.94
A-99		387.32	388	C	2.03

TABLE 2-continued

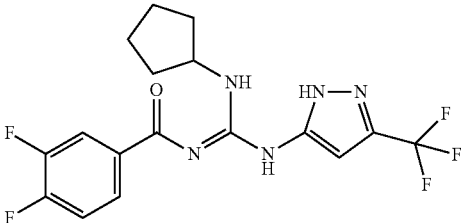
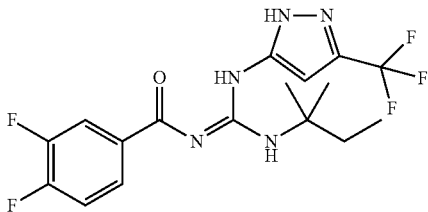
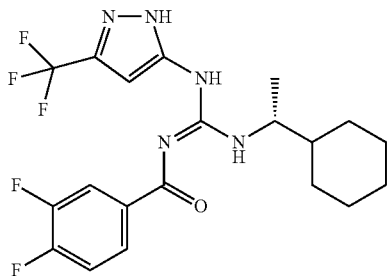
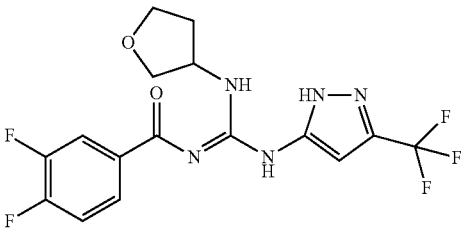
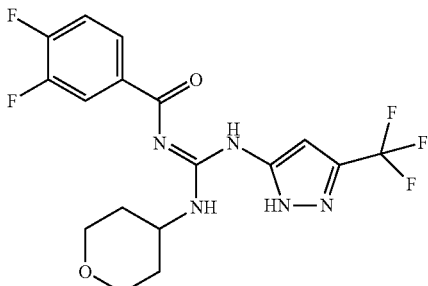
Compound No.	Chemical Structure	Calculated	MS (m/z)	HPLC Method	HPLC Retention
		MW (g/mol)			Time (min)
A-100		401.34	402	C	2.11
A-101		403.36	404	C	2.67
A-102		443.42	444	C	2.51
A-103		403.31	404	C	1.92
A-104		417.34	418	C	1.92

TABLE 2-continued

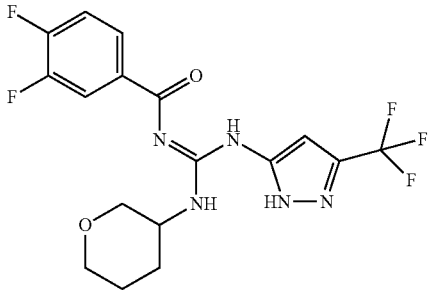
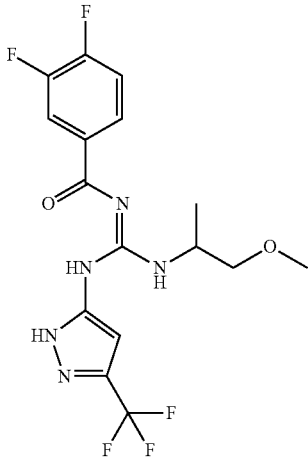
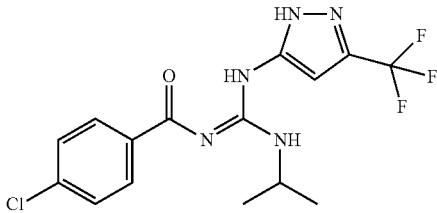
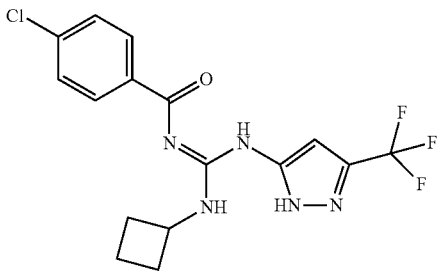
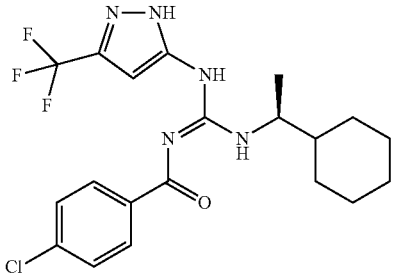
Compound No.	Chemical Structure	Calculated MW (g/mol)	MS (m/z)	HPLC Method	HPLC Retention Time (min)
A-105		417.34	418	C	1.99
A-106		405.33	406	C	1.95
A-107		373.77	374	C	1.9
A-108		385.78	386	C	1.98
A-109		441.89	442	C	2.43

TABLE 2-continued

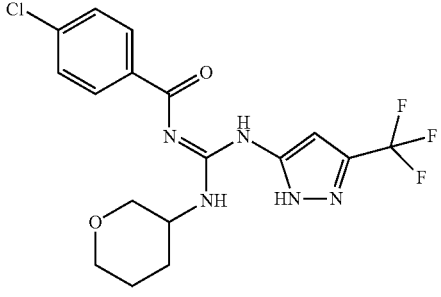
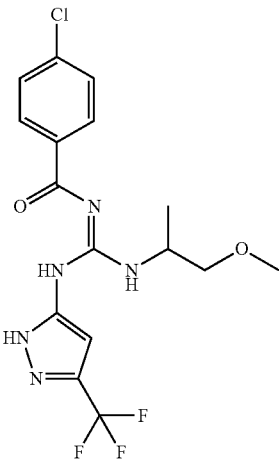
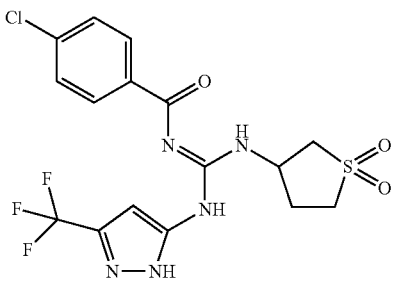
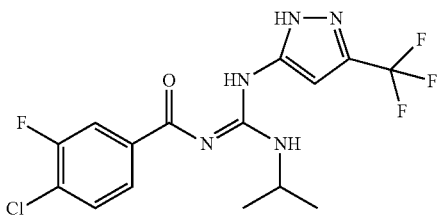
Compound No.	Chemical Structure	Calculated MW (g/mol)	MS (m/z)	HPLC Method	HPLC Retention Time (min)
A-110		415.81	416	C	1.93
A-111		403.79	404	C	1.91
A-112		449.84	450	C	1.99
A-113		391.76	392	C	2.13

TABLE 2-continued

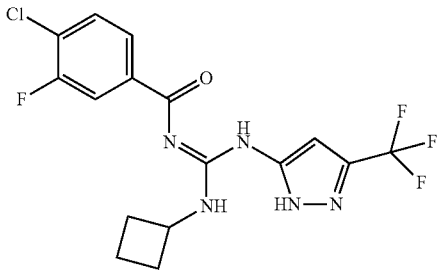
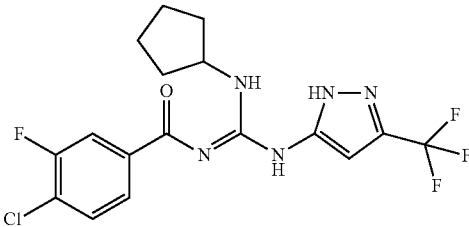
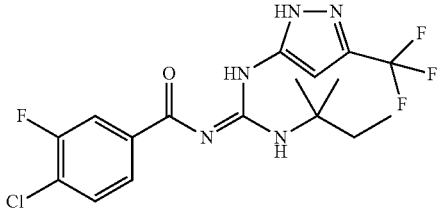
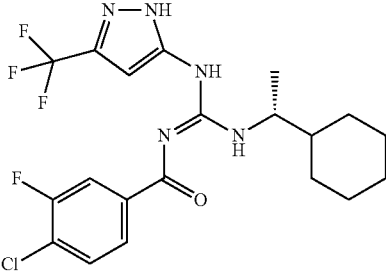
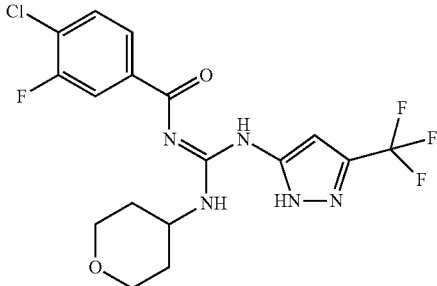
Compound No.	Chemical Structure	Calculated	MS	HPLC Method	HPLC Retention
		MW (g/mol)	(m/z)		Time (min)
A-114		403.77	404	C	2.23
A-115		417.8	418.40	C	2.31
A-116		419.81	420	C	2.89
A-117		459.88	460	C	2.7
A-118		433.8	434	C	2.1



TABLE 2-continued

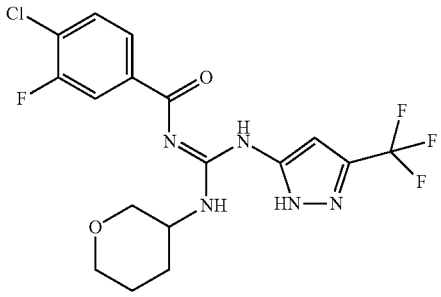
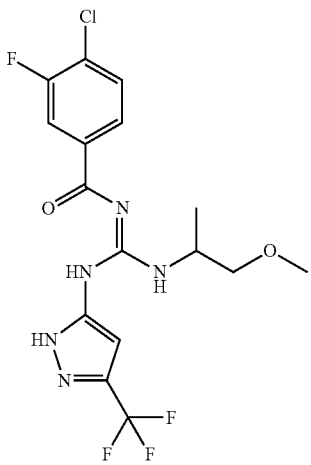
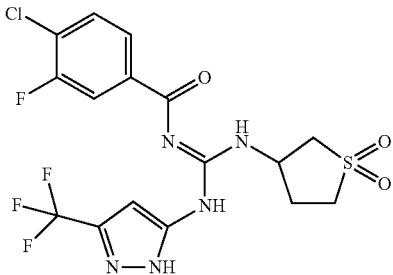
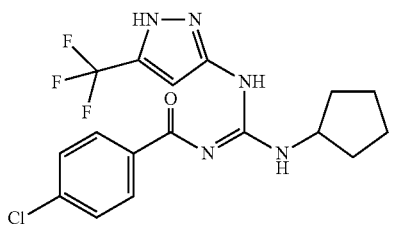
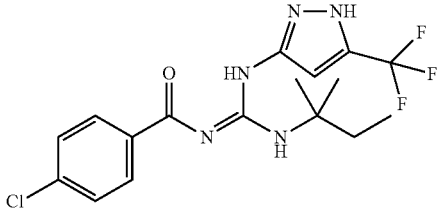
Compound No.	Chemical Structure	Calculated MW (g/mol)	MS (m/z)	HPLC Method	HPLC Retention Time (min)
A-119		433.8	434	C	2.19
A-120		421.79	422	C	2.24
A-121		467.83	468	C	2.17
A-122		399.81	400	C	2.09
A-123		401.82	402	C	2.67

TABLE 2-continued

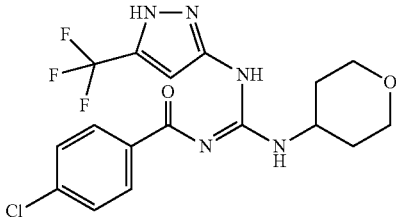
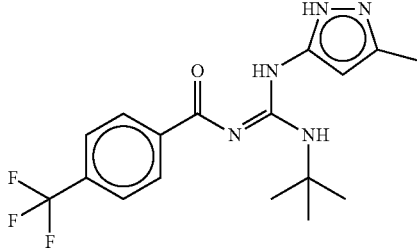
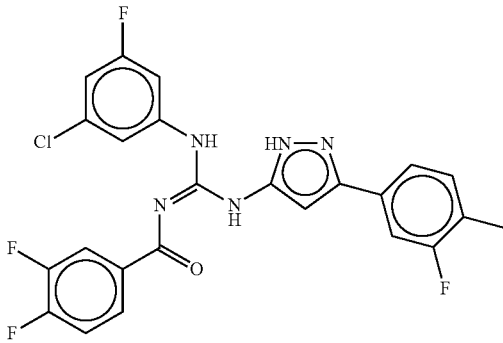
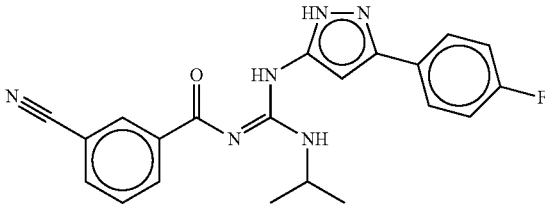
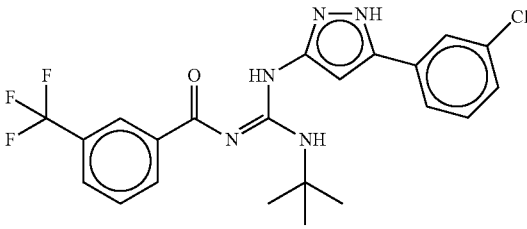
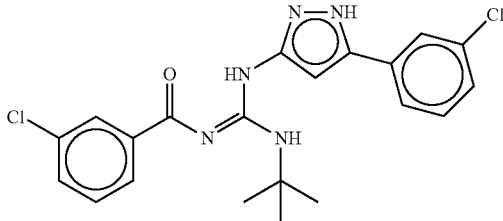
Compound No.	Chemical Structure	Calculated MW (g/mol)	MS (m/z)	HPLC Method	HPLC Retention Time (min)
A-124		415.81	416	C	1.9
A-125		367.37	390 (M + Na)	E	5.84
A-126		501.86	502	D	3.26
A-127		390.41	391	E	4.9
A-128		463.88	464	NA	NA
A-129		430.33	431	D	2.71

TABLE 2-continued

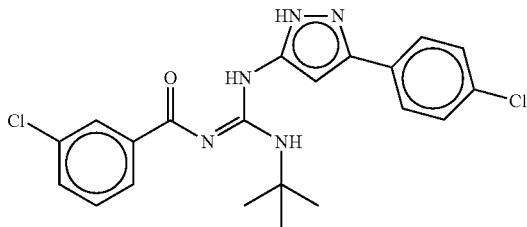
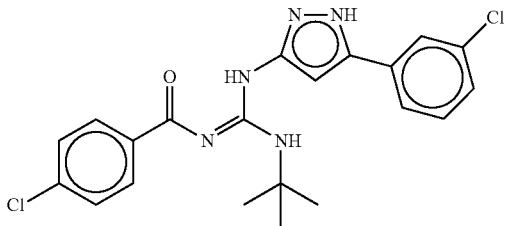
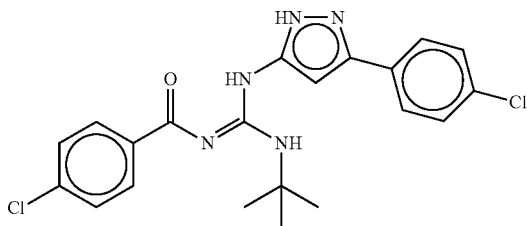
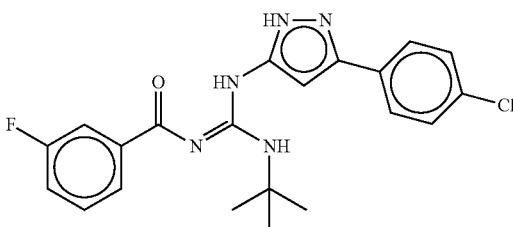
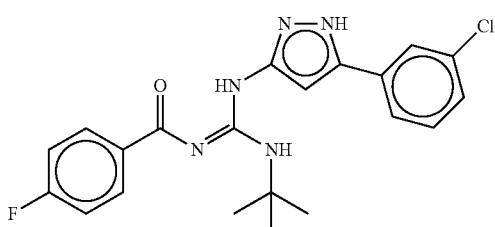
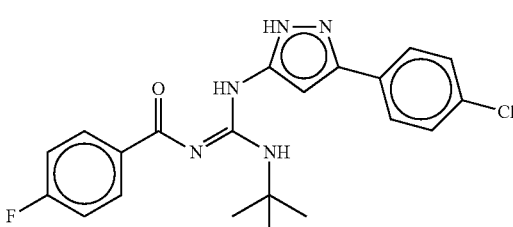
Compound No.	Chemical Structure	Calculated MW (g/mol)	MS (m/z)	HPLC Method	HPLC Retention Time (min)
A-130		430.33	431	D	2.69
A-131		430.33	431	D	2.6
A-132		430.33	431	D	2.57
A-133		413.88	414	D	2.49
A-134		413.88	414	D	2.37
A-135		413.88	414	D	2.36

TABLE 2-continued

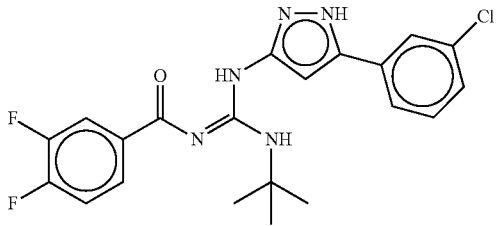
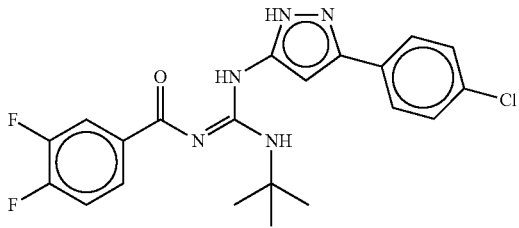
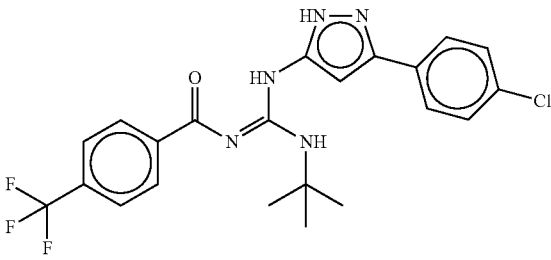
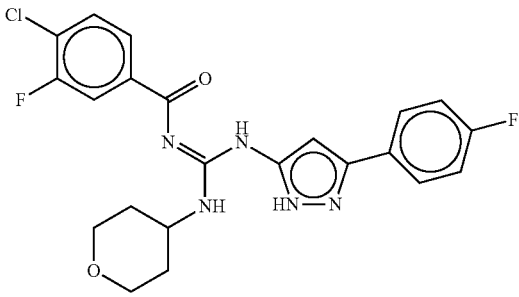
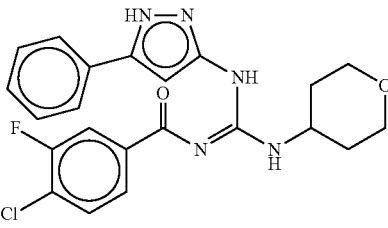
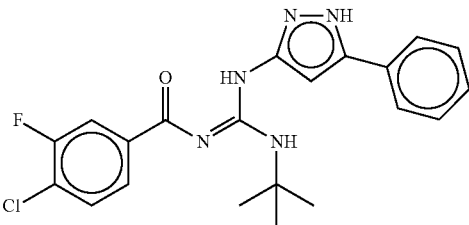
Compound No.	Chemical Structure	Calculated MW (g/mol)	MS (m/z)	HPLC Method	HPLC Retention Time (min)
A-136		431.87	432	D	2.75
A-137		431.87	432	D	2.72
A-138		463.88	464	D	2.83
A-139		459.88	460	D	2.21
A-140		441.89	442	D	2.16
A-141		413.88	414	D	2.77

TABLE 2-continued

Compound No.	Chemical Structure	Calculated MW (g/mol)	MS (m/z)	HPLC Method	HPLC Retention Time (min)
A-142		518.32	518	D	2.83
A-143		500.33	500	D	2.79
A-144		492.33	492	D	3.28
A-145		504.29	504	D	3.31
A-146		450.27	450	D	3.11
A-147		464.3	464	D	3.24

TABLE 2-continued

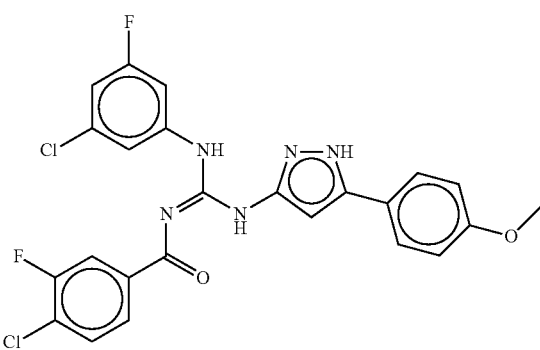
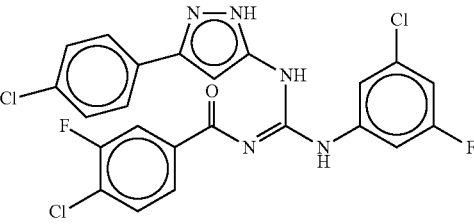
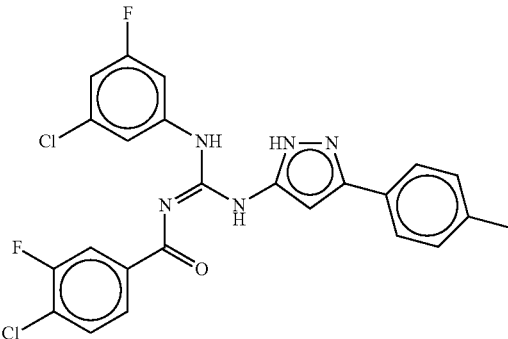
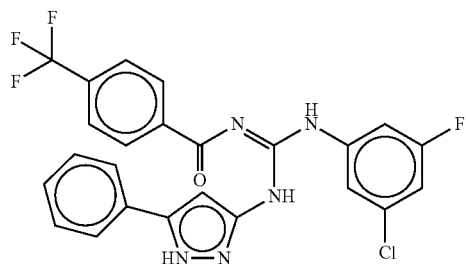
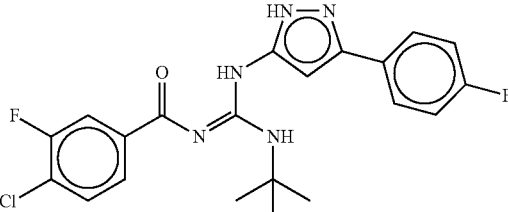
Compound No.	Chemical Structure	Calculated MW (g/mol)	MS (m/z)	HPLC Method	HPLC Retention Time (min)
A-148		516.33	516	D	3.28
A-149		520.75	522	D	3.42
A-150		500.33	500	D	3.38
A-151		501.86	502	D	3.22
A-152		431.87	432	D	2.8

TABLE 2-continued

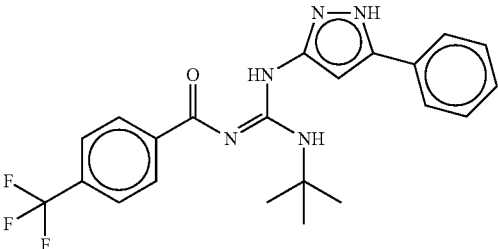
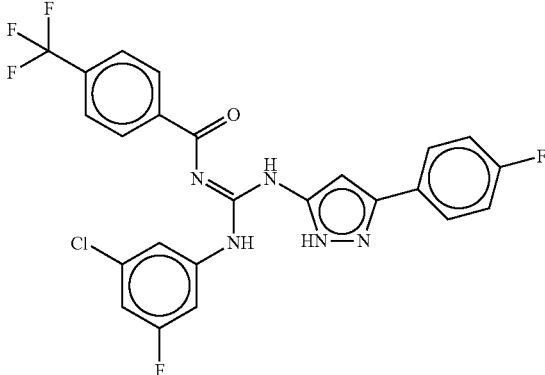
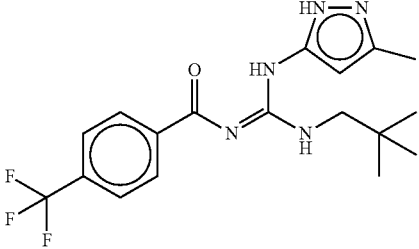
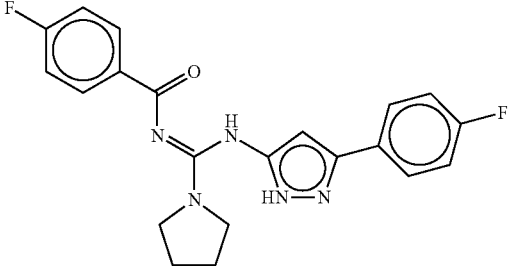
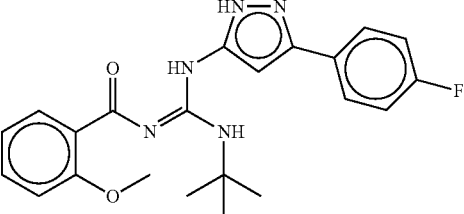
Compound No.	Chemical Structure	Calculated MW (g/mol)	MS (m/z)	HPLC Method	HPLC Retention Time (min)
A-153		429.44	430	D	2.68
A-154		519.85	520	D	3.24
A-155		381.4	382.13, 404.13	B	5.169
A-156		395.41	396.04, 418.00	E	4.077
A-157		409.46	410.07, 432.04	E	5.088

TABLE 2-continued

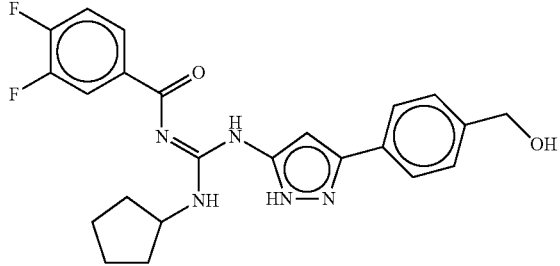
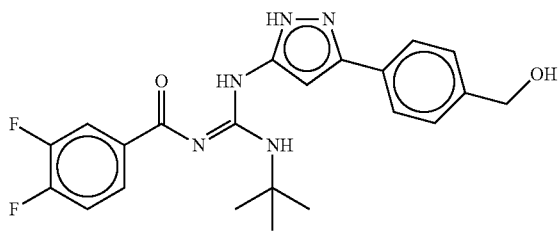
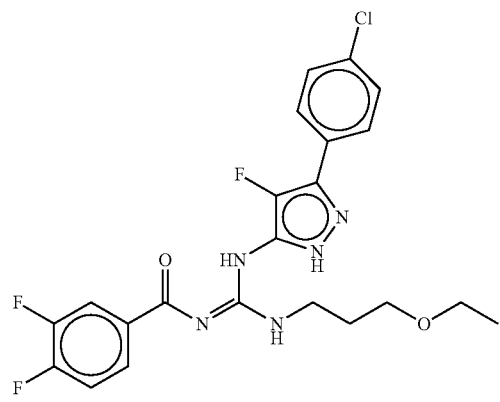
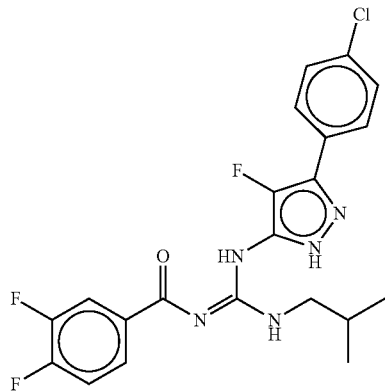
Compound No.	Chemical Structure	Calculated	MS (m/z)	HPLC Method	HPLC Retention
		MW (g/mol)			Time (min)
A-158		439.46	440.09	B	4.777
A-159		427.45	428.13, 450.10	B	5.66
A-160		479.88	434.05, 436.06	B	6.57
A-161		449.86	NA	NA	NA



TABLE 2-continued

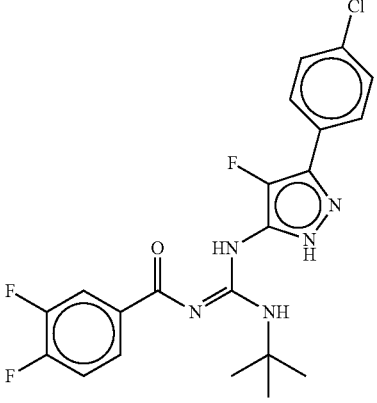
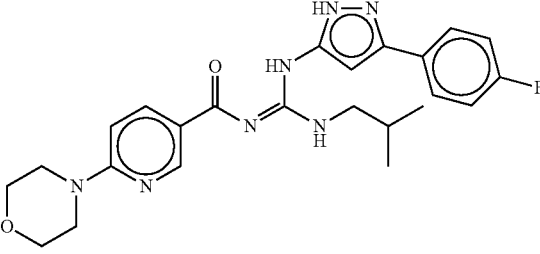
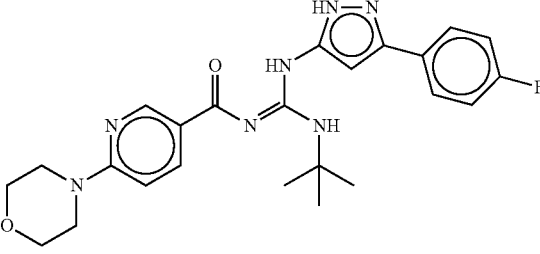
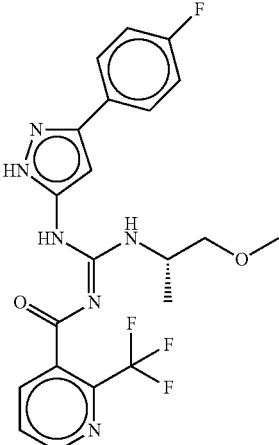
Compound No.	Chemical Structure	Calculated	MS (m/z)	HPLC Method	HPLC Retention
		MW (g/mol)			Time (min)
A-162		449.86	450.10, 472.06	B	7.88
A-163		465.52	466.15, 488.05	B	4.89
A-164		465.52	466.15, 488.11	B	4.66
A-165		464.42	NA	NA	NA

TABLE 2-continued

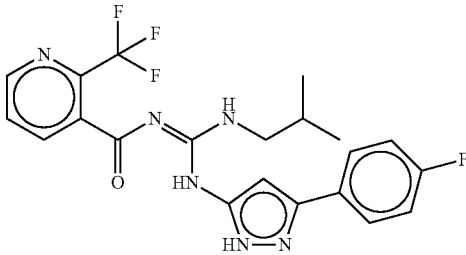
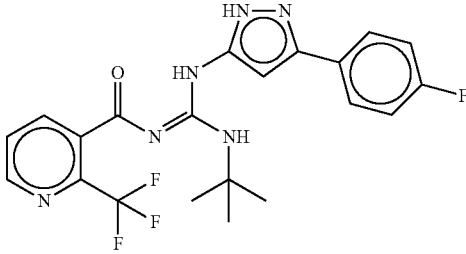
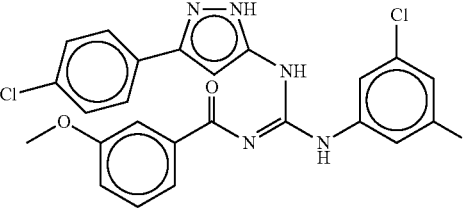
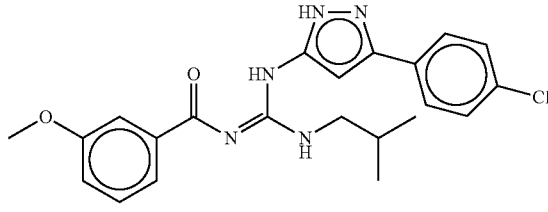
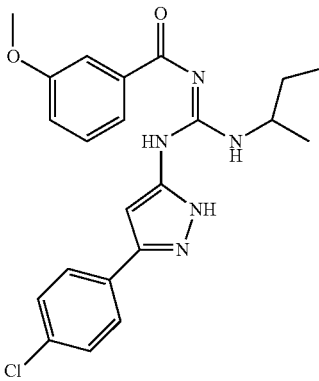
Compound No.	Chemical Structure	Calculated	MS	HPLC	HPLC
		MW (g/mol)	(m/z)	Method	Retention Time (min)
A-166		448.42	NA	NA	NA
A-167		448.42	NA	NA	NA
A-168		498.34	NA	NA	NA
A-169		425.91	NA	NA	NA
A-170		425.91	NA	NA	NA

TABLE 2-continued

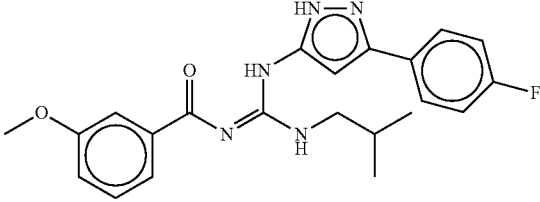
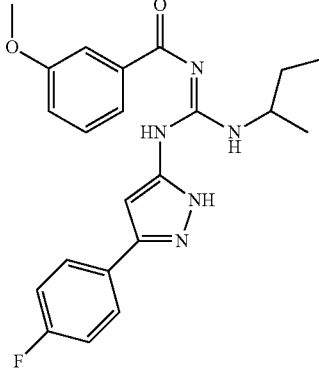
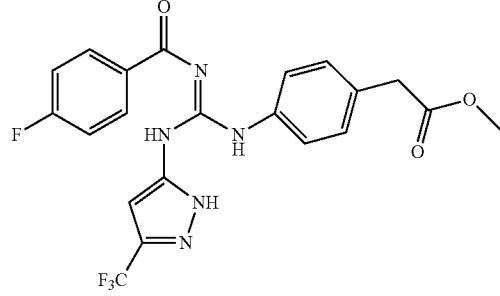
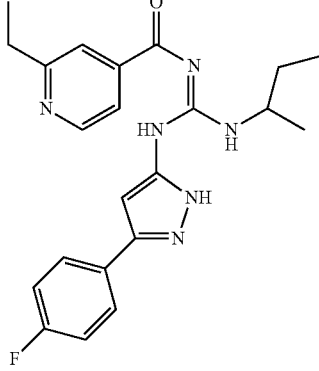
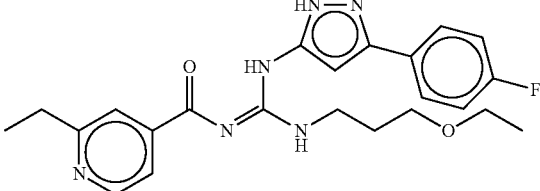
Compound No.	Chemical Structure	Calculated MW (g/mol)	MS (m/z)	HPLC Method	HPLC Retention Time (min)
A-171		409.46	410.14	B	5.13
A-172		409.46	NA	NA	NA
A-173		463.39	464.07, 486.03	B	5.33
A-174		408.47	409.16	B	4.68
A-175		438.5	NA	NA	NA

TABLE 2-continued

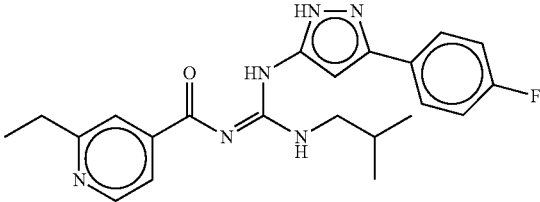
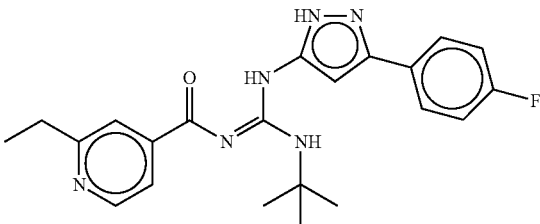
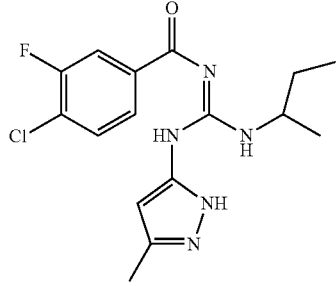
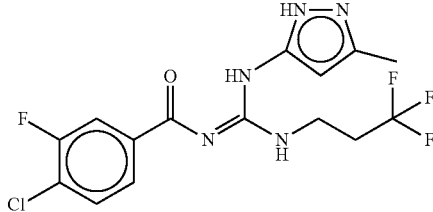
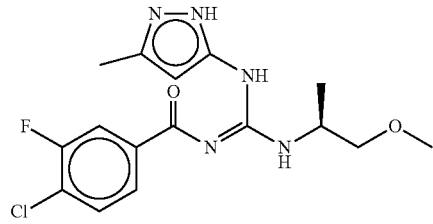
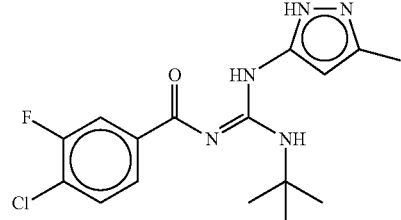
Compound No.	Chemical Structure	Calculated MW (g/mol)	MS (m/z)	HPLC Method	HPLC Retention Time (min)
A-176		408.47	409.16	B	4.7
A-177		408.47	409.16, 431.12	B	4.76
A-178		351.81	NA	NA	NA
A-179		391.75	NA	NA	NA
A-180		381.83	NA	NA	NA
A-181		351.81	NA	NA	NA

TABLE 2-continued

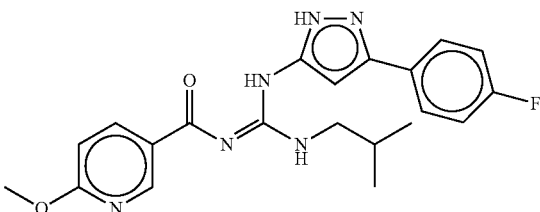
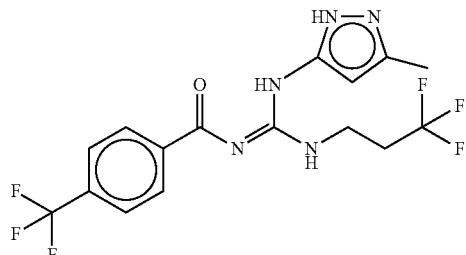
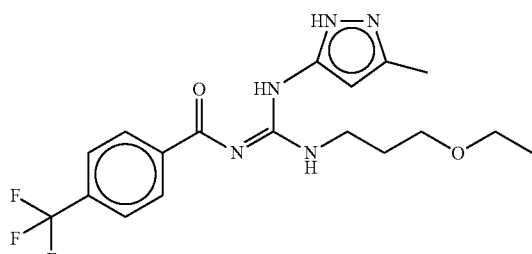
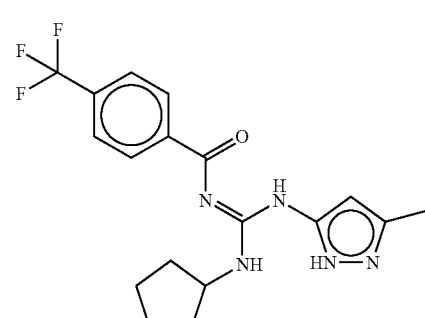
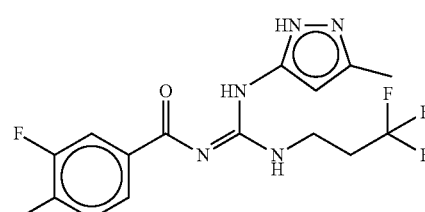
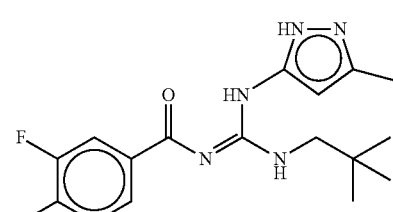
Compound No.	Chemical Structure	Calculated MW (g/mol)	MS (m/z)	HPLC Method	HPLC Retention Time (min)
A-182		410.44	411.11, 433.14	B	4.95
A-183		407.31	NA	NA	NA
A-184		397.39	NA	NA	NA
A-185		379.38	NA	NA	NA
A-186		375.3	NA	NA	NA
A-187		349.38	NA	NA	NA

TABLE 2-continued

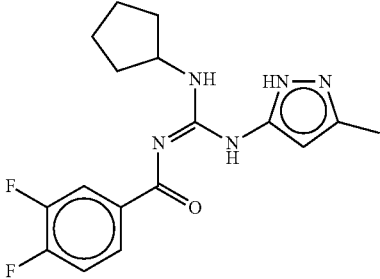
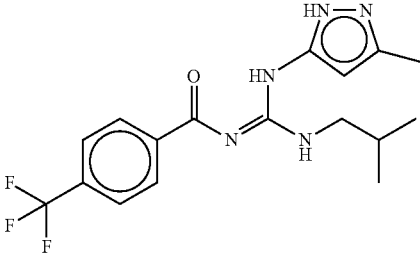
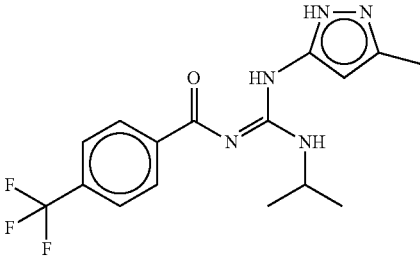
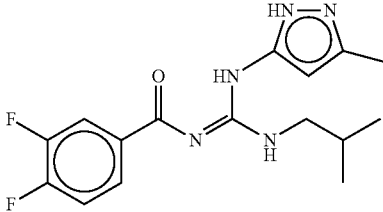
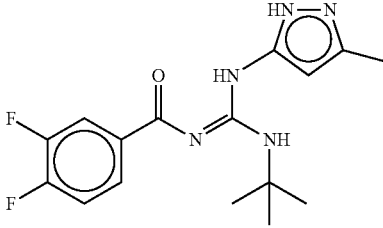
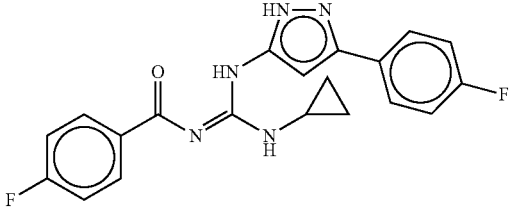
Compound No.	Chemical Structure	Calculated MW (g/mol)	MS (m/z)	HPLC Method	HPLC Retention Time (min)
A-188		347.36	NA	NA	NA
A-189		367.37	NA	NA	NA
A-190		353.34	NA	NA	NA
A-191		335.35	NA	NA	NA
A-192		335.35	NA	NA	NA
A-193		381.38	NA	NA	NA

TABLE 2-continued

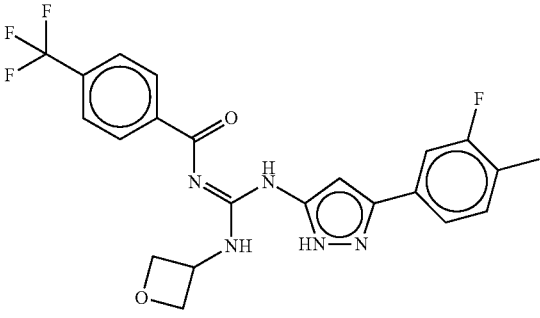
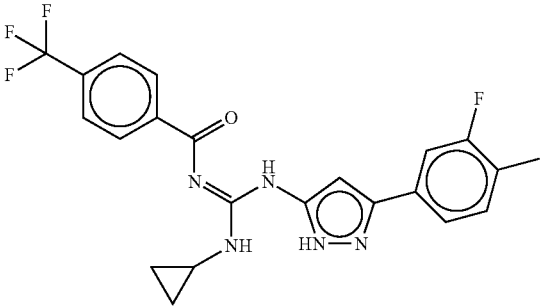
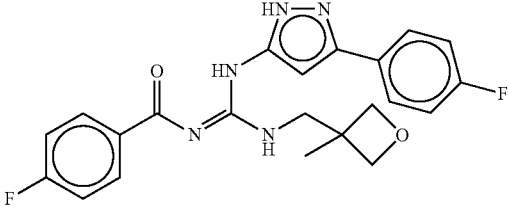
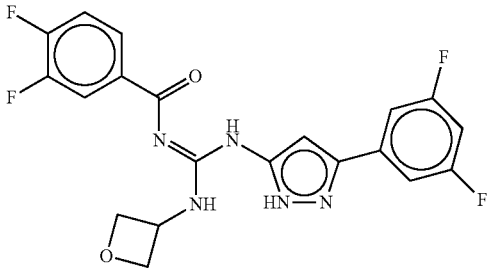
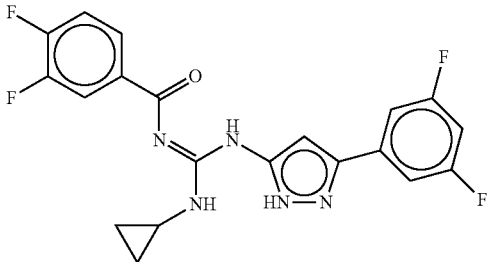
Compound No.	Chemical Structure	Calculated	MS (m/z)	HPLC Method	HPLC Retention
		MW (g/mol)			Time (min)
A-194		461.41	NA	NA	NA
A-195		445.41	NA	NA	NA
A-196		425.43	NA	NA	NA
A-197		433.36	NA	NA	NA
A-198		417.36	NA	NA	NA

TABLE 2-continued

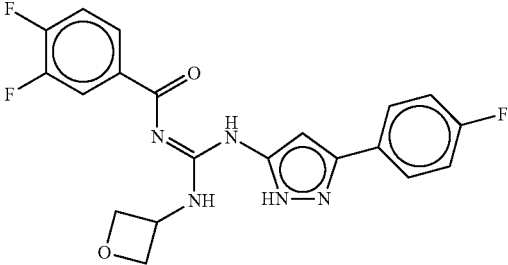
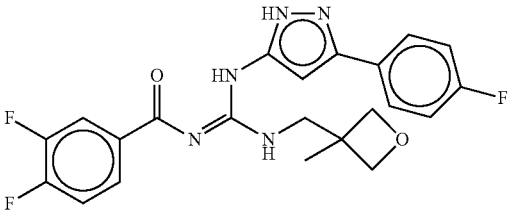
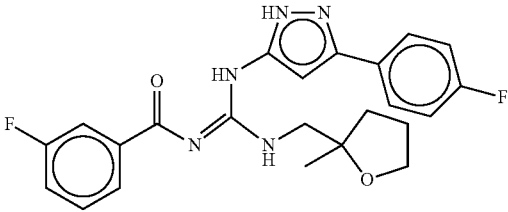
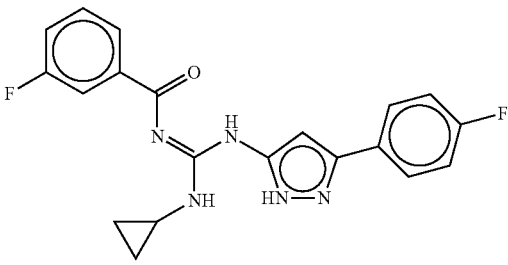
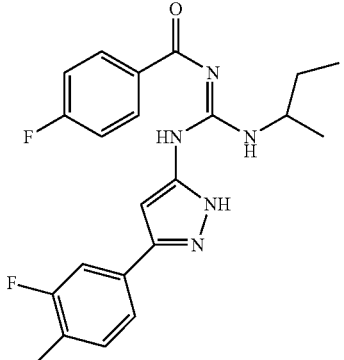
Compound No.	Chemical Structure	Calculated	MS (m/z)	HPLC Method	HPLC Retention
		MW (g/mol)			Time (min)
A-199		415.37	NA	NA	NA
A-200		443.42	NA	NA	NA
A-201		439.46	NA	NA	NA
A-202		381.38	NA	NA	NA
A-203		411.45	NA	NA	NA



TABLE 2-continued

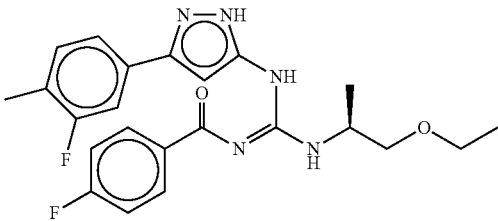
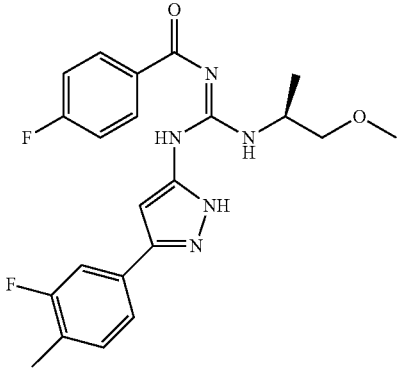
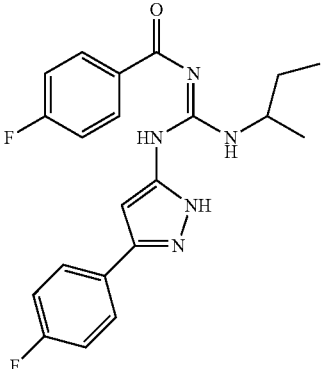
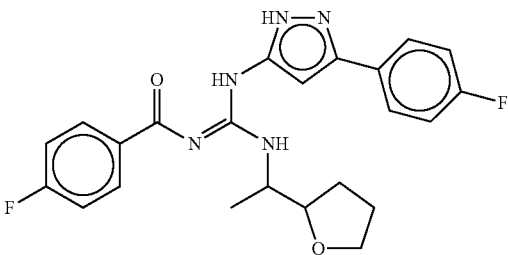
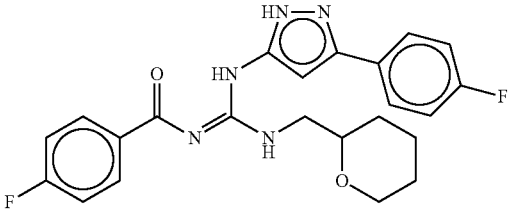
Compound No.	Chemical Structure	Calculated MW (g/mol)	MS (m/z)	HPLC Method	HPLC Retention Time (min)
A-204		441.47	NA	NA	NA
A-205		427.45	NA	NA	NA
A-206		397.42	420.08	B	5.09
A-207		439.46	NA	NA	NA
A-208		439.46	NA	NA	NA

TABLE 2-continued

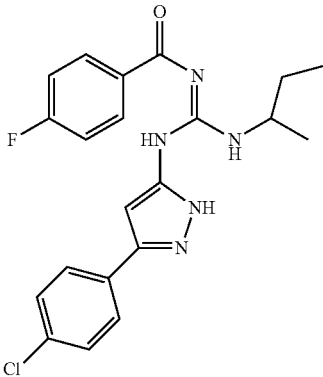
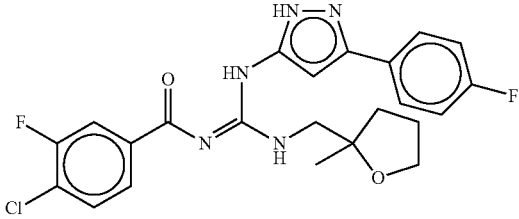
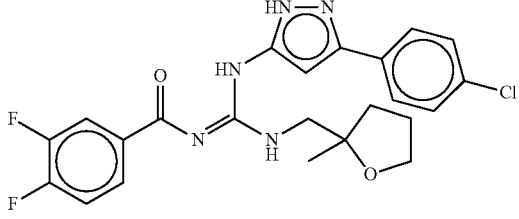
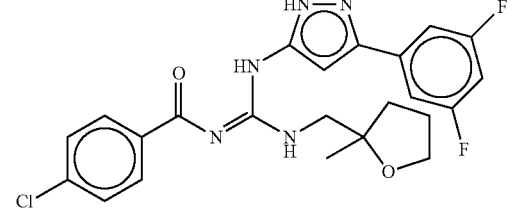
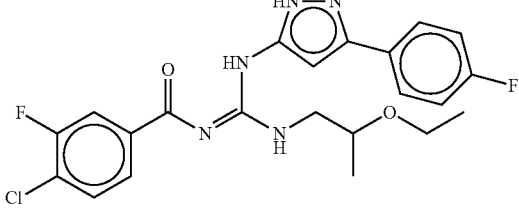
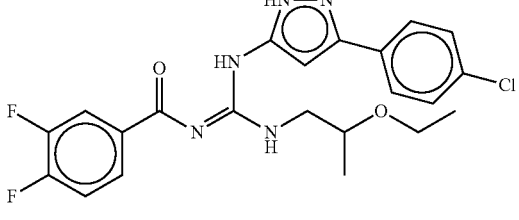
Compound No.	Chemical Structure	Calculated MW (g/mol)	MS (m/z)	HPLC Method	HPLC Retention Time (min)
A-209		413.88	414.03, 436.06	B	5.3
A-210		473.9	NA	NA	NA
A-211		473.9	NA	NA	NA
A-212		473.9	NA	NA	NA
A-213		461.89	462.05	B	5.61
A-214		461.89	462.05	B	5.56

TABLE 2-continued

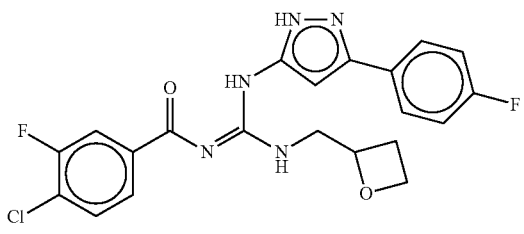
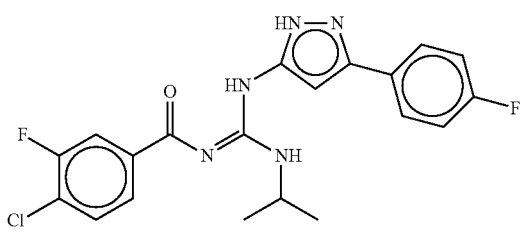
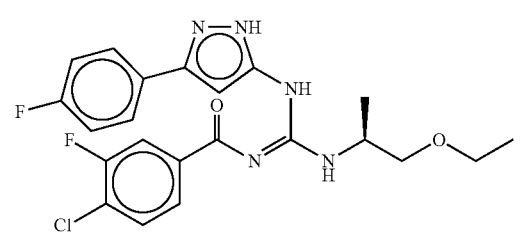
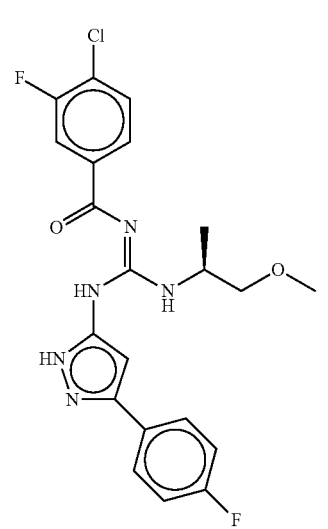
Compound No.	Chemical Structure	Calculated	MS	HPLC	HPLC
		MW (g/mol)	(m/z)	Method	Retention Time (min)
A-215		445.85	NA	NA	NA
A-216		417.84	418.00, 440.03	B	5.47
A-217		461.89	NA	NA	NA
A-218		447.87	448.02	B	5.49

TABLE 2-continued

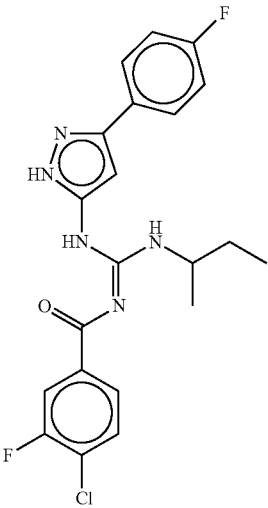
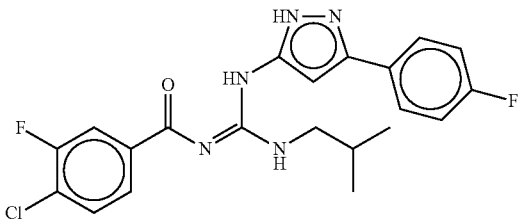
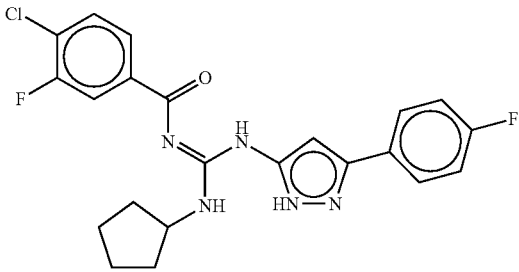
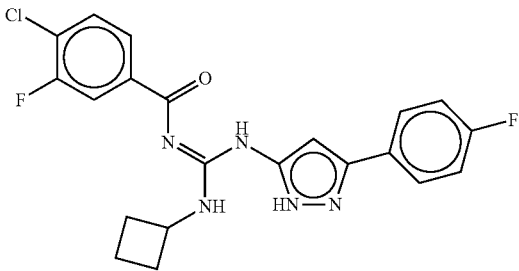
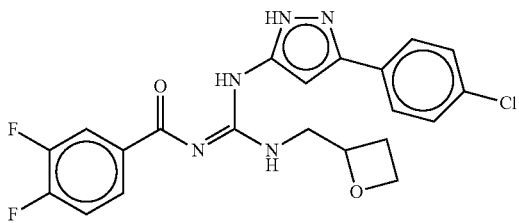
Compound No.	Chemical Structure	Calculated MW (g/mol)	MS (m/z)	HPLC Method	HPLC Retention Time (min)
A-219		431.87	432.03, 454.00	B	5.75
A-220		431.87	432.03, 454.00	B	5.73
A-221		443.88	444.05, 466.02	B	5.79
A-222		429.85	430.02, 451.98	B	5.64
A-223		445.85	NA	NA	NA

TABLE 2-continued

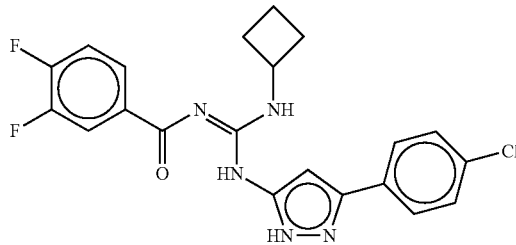
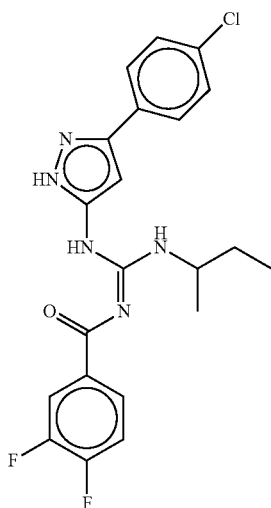
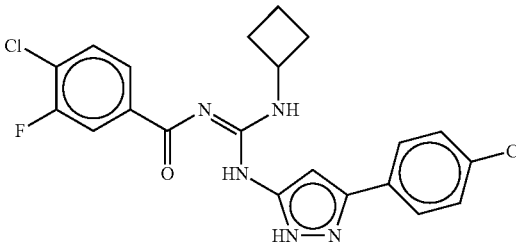
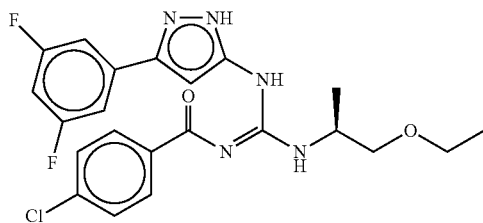
Compound No.	Chemical Structure	Calculated	MS	HPLC	HPLC
		MW (g/mol)	(m/z)	Method	Retention Time (min)
A-224		429.85	NA	NA	NA
A-225		431.87	432.03, 454.00	B	5.65
A-226		446.31	NA	NA	NA
A-227		461.89	NA	NA	NA

TABLE 2-continued

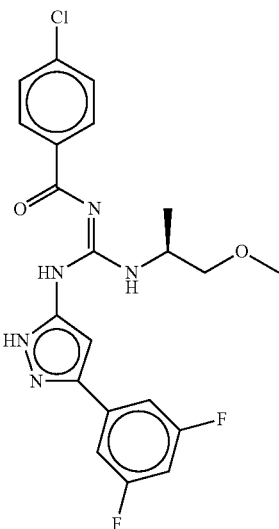
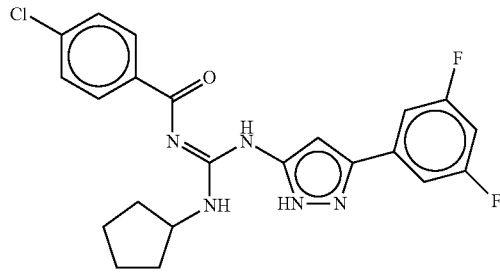
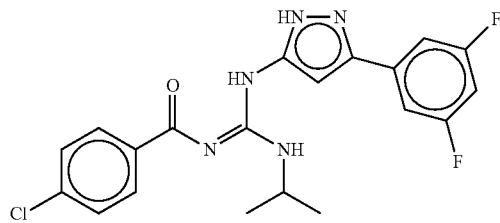
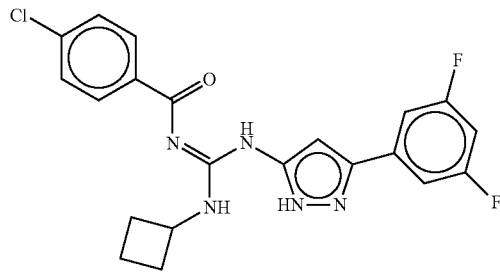
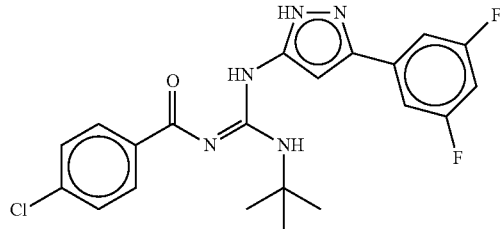
Compound No.	Chemical Structure	Calculated MW (g/mol)	MS (m/z)	HPLC Method	HPLC Retention Time (min)
A-228		447.87	NA	NA	NA
A-229		443.88	NA	NA	NA
A-230		417.84	418.06, 440.03	B	5.27
A-231		429.85	430.02, 451.98	B	5.37
A-232		431.87	NA	NA	NA

TABLE 2-continued

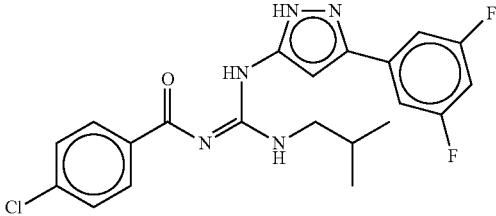
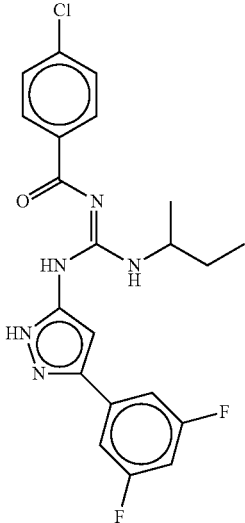
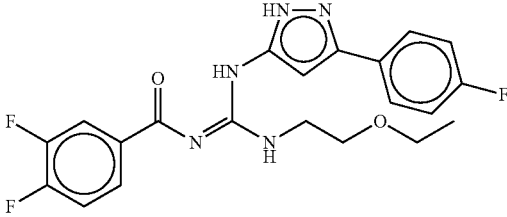
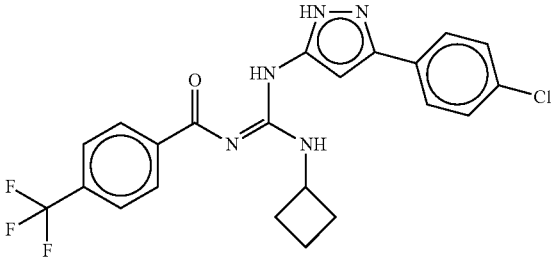
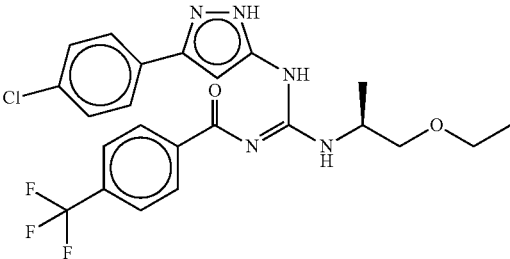
Compound No.	Chemical Structure	Calculated MW (g/mol)	MS (m/z)	HPLC Method	HPLC Retention Time (min)
A-233		431.87	432.03, 454.06	B	5.5
A-234		431.87	432.03, 454.06	B	5.44
A-235		431.41	432.10, 454.06	B	5.04
A-236		461.87	NA	NA	NA
A-237		493.91	NA	NA	NA

TABLE 2-continued

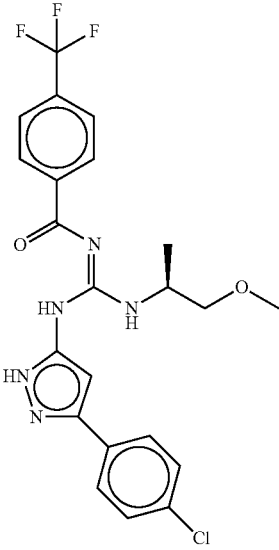
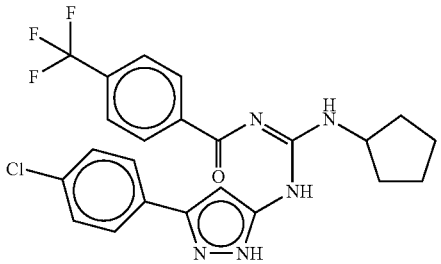
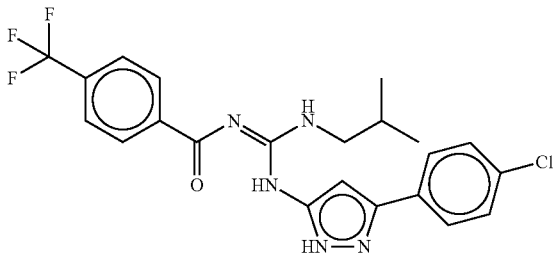
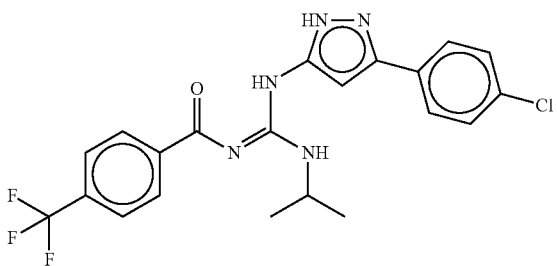
Compound No.	Chemical Structure	Calculated	MS (m/z)	HPLC Method	HPLC Retention
		MW (g/mol)			Time (min)
A-238		479.88	NA	NA	NA
A-239		475.89	NA	NA	NA
A-240		463.88	464.00, 485.97	B	5.86
A-241		449.86	449.97, 472.00	B	5.63



TABLE 2-continued

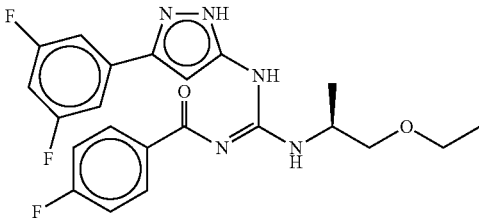
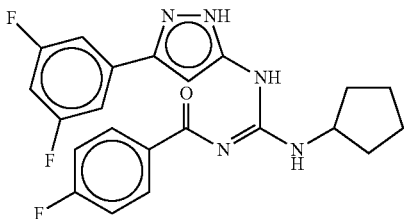
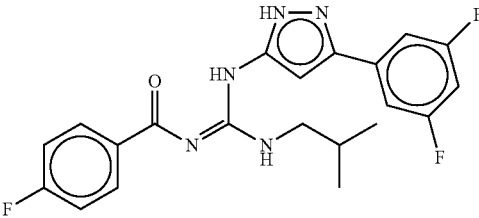
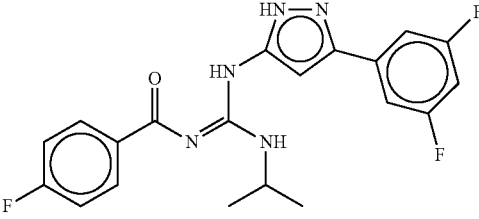
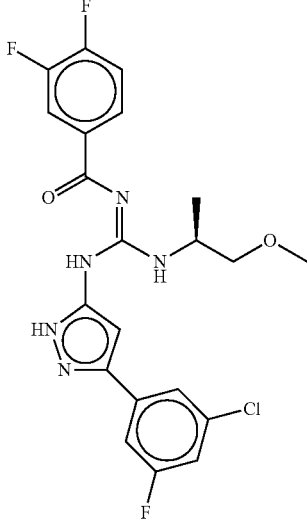
Compound No.	Chemical Structure	Calculated MW (g/mol)	MS (m/z)	HPLC Method	HPLC Retention Time (min)
A-242		445.44	446.07, 468.03	B	5.24
A-243		427.42	428.07, 450.03	B	5.31
A-244		415.41	416.05, 438.08	B	5.24
A-245		401.39	402.08, 424.11	B	4.99
A-246		465.86	466.02, 487.98	B	5.64

TABLE 2-continued

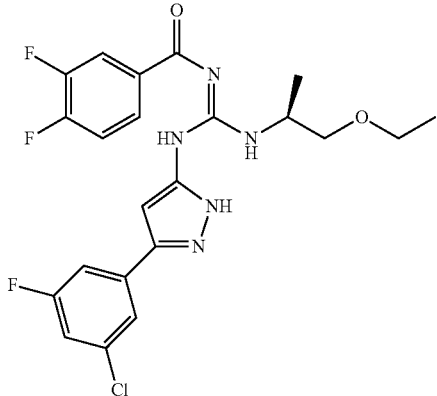
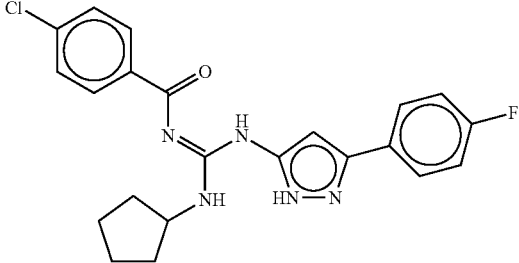
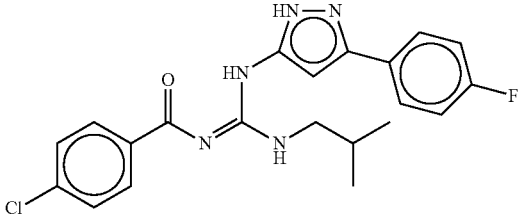
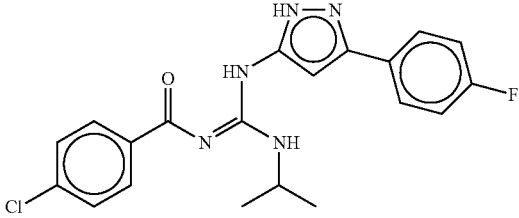
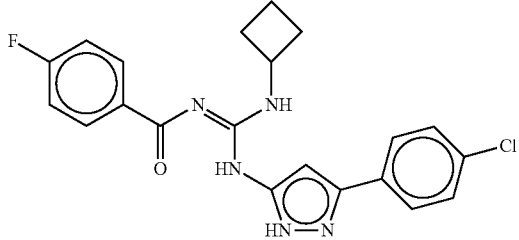
Compound No.	Chemical Structure	Calculated	MS (m/z)	HPLC Method	HPLC Retention
		MW (g/mol)			Time (min)
A-247		479.88	NA	NA	NA
A-248		425.89	NA	NA	NA
A-249		413.88	414.03, 436.06	B	5.4
A-250		399.85	400.06, 422.03	B	5.14
A-251		411.86	NA	NA	NA

TABLE 2-continued

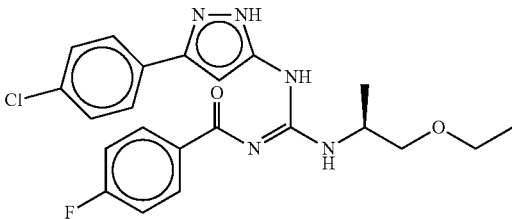
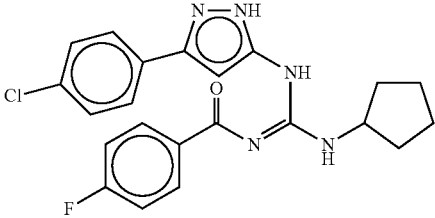
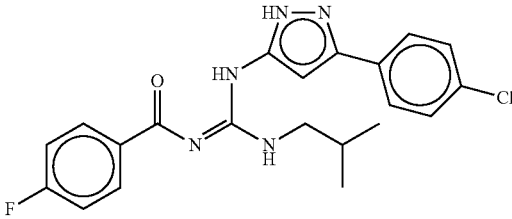
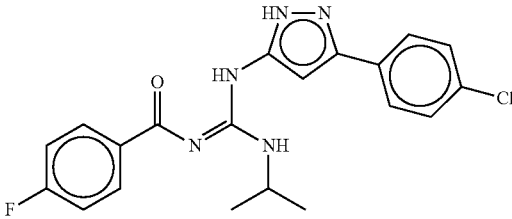
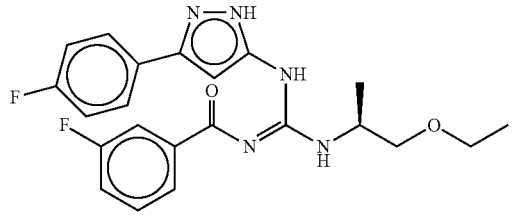
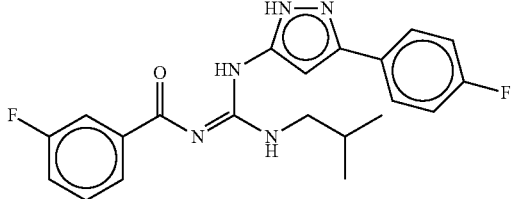
Compound No.	Chemical Structure	Calculated	MS	HPLC	HPLC
		MW (g/mol)	(m/z)	Method	Retention Time (min)
A-252		443.9	NA	NA	NA
A-253		425.89	NA	NA	NA
A-254		413.88	414.10, 436.06	B	5.33
A-255		399.85	400.06, 422.03	B	5.08
A-256		427.45	428.13, 450.10	B	5.18
A-257		397.42	398.12, 420.08	B	5.16

TABLE 2-continued

Compound No.	Chemical Structure	Calculated MW (g/mol)	MS (m/z)	HPLC Method	HPLC Retention Time (min)
A-258		461.89	462.05, 484.02	B	5.66
A-259		413.4	414.03, 436.06	B	5.27
A-260		427.42	428.07, 451.07	B	5.44
A-261		415.41	416.05, 438.08	B	5.37
A-262		401.39	NA	NA	NA
A-263		445.44	446.07, 468.03	B	5.39

TABLE 2-continued

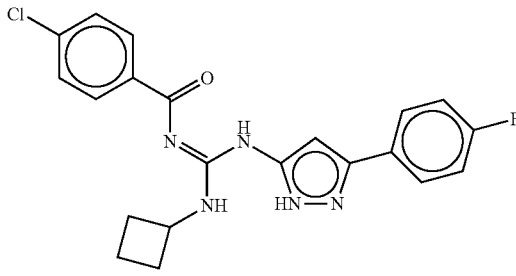
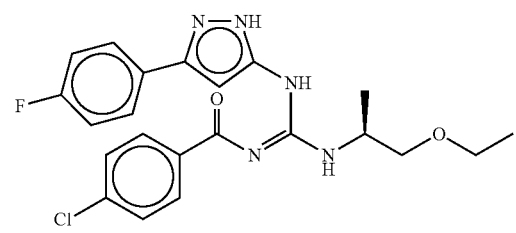
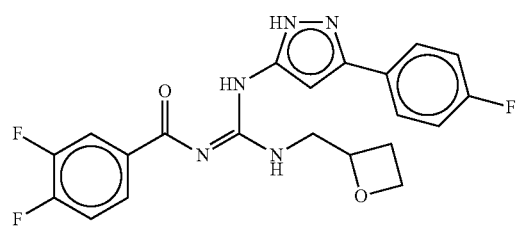
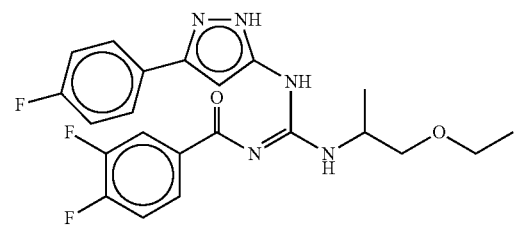
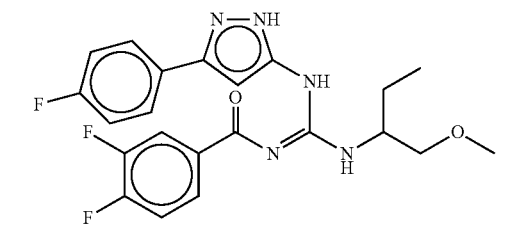
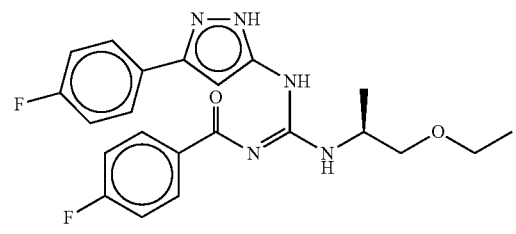
Compound No.	Chemical Structure	Calculated MW (g/mol)	MS (m/z)	HPLC Method	HPLC Retention Time (min)
A-264		411.86	412.09, 434.05	B	5.26
A-265		443.9	NA	NA	NA
A-266		429.4	NA	NA	NA
A-267		445.44	446.13	B	5.41
A-268		445.44	446.07	B	5.43
A-269		427.45	NA	NA	NA

TABLE 2-continued

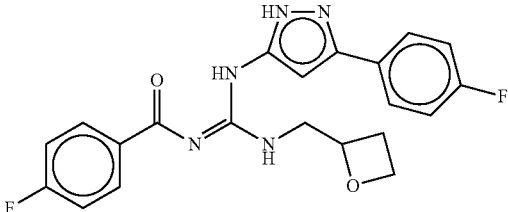
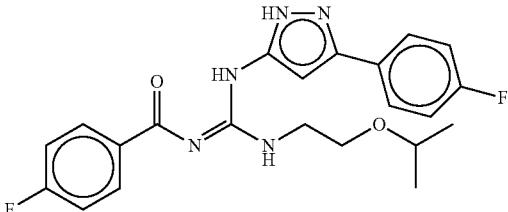
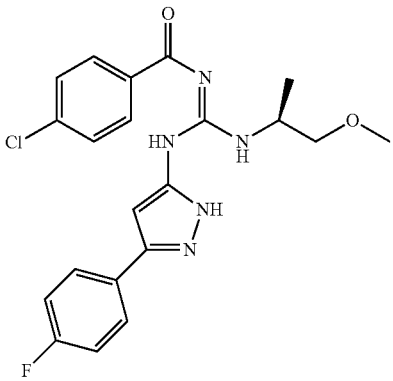
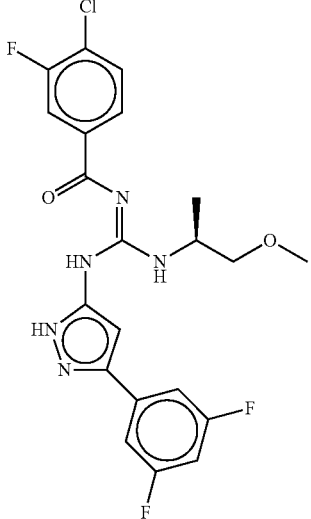
Compound No.	Chemical Structure	Calculated	MS (m/z)	HPLC Method	HPLC Retention
		MW (g/mol)			Time (min)
A-270		411.4	NA	NA	NA
A-271		427.45	NA	NA	NA
A-272		429.88	NA	NA	NA
A-273		465.86	NA	NA	NA

TABLE 2-continued

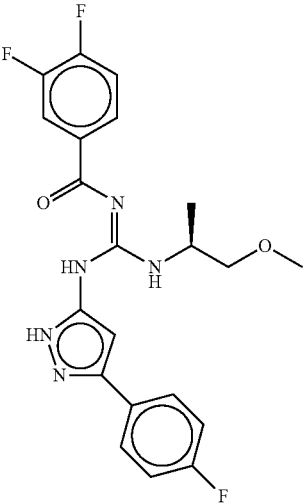
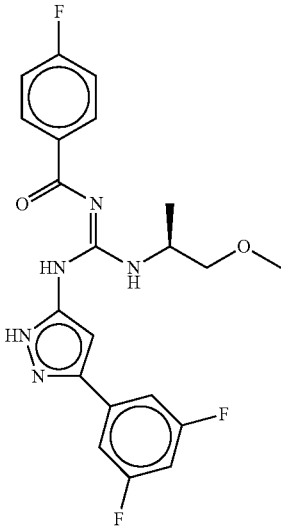
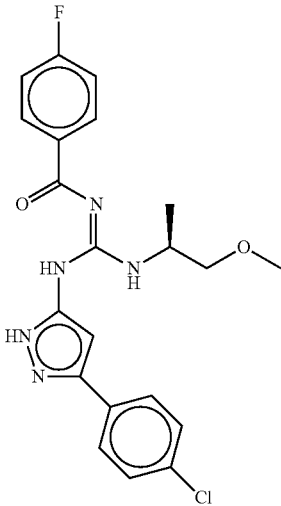
Compound No.	Chemical Structure	Calculated MW (g/mol)	MS (m/z)	HPLC Method	HPLC Retention Time (min)
A-274		431.41	432.03, 454.06	B	5.15
A-275		431.41	NA	NA	NA
A-276		429.88	NA	NA	NA

TABLE 2-continued

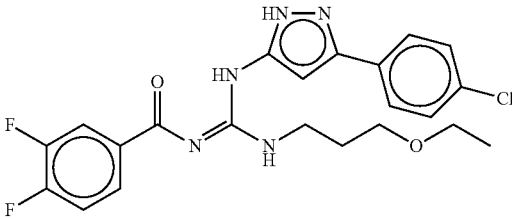
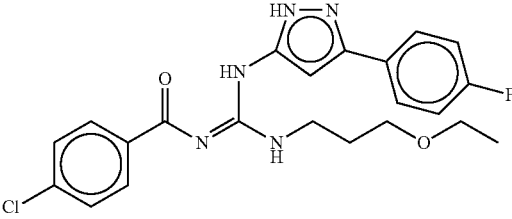
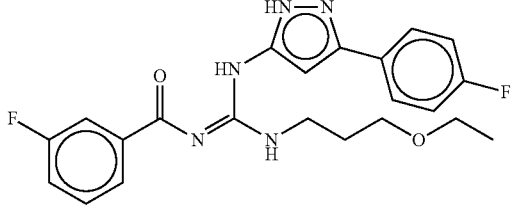
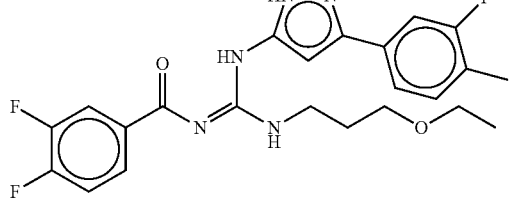
Compound No.	Chemical Structure	Calculated MW (g/mol)	MS (m/z)	HPLC Method	HPLC Retention Time (min)
A-277		461.89	NA	NA	NA
A-278		443.9	NA	NA	NA
A-279		427.45	NA	NA	NA
A-280		427.45	NA	NA	NA
A-281		459.46	NA	NA	NA
A-282		495.45	496.04, 518.01	B	5.6



TABLE 2-continued

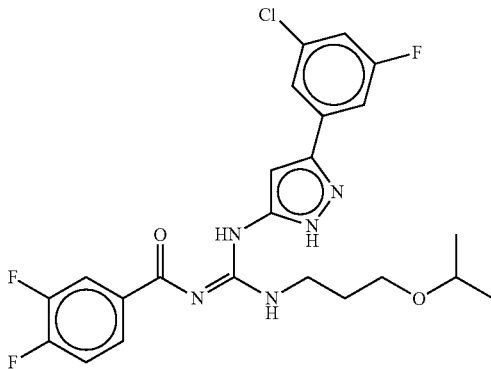
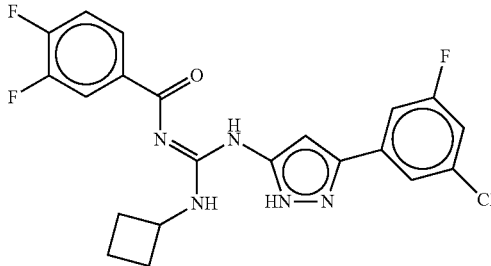
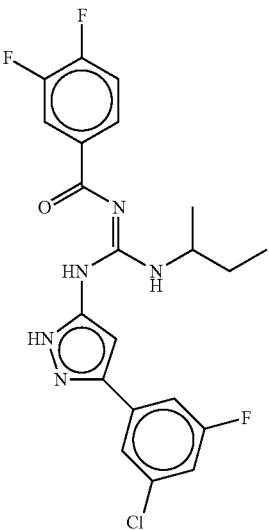
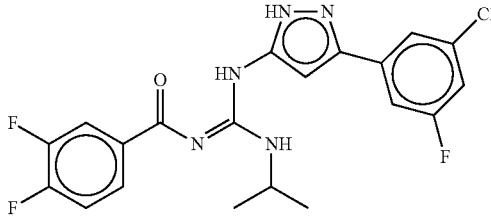
Compound No.	Chemical Structure	Calculated	MS	HPLC	HPLC
		MW (g/mol)	(m/z)	Method	Retention Time (min)
A-283		493.91	494.03	B	5.8
A-284		447.84	447.95, 469.98	B	5.77
A-285		449.86	449.97, 472.00	B	5.87
A-286		435.83	436.00, 457.96	B	5.59

TABLE 2-continued

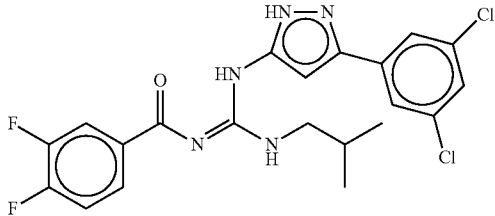
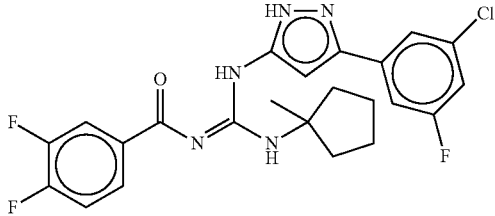
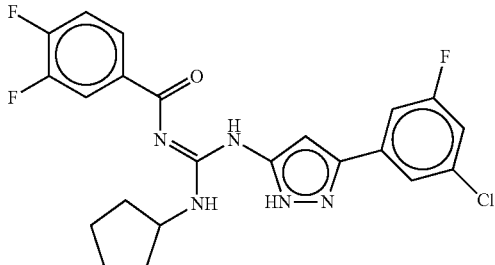
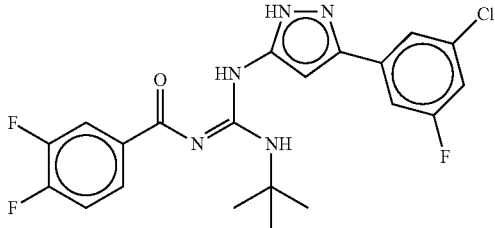
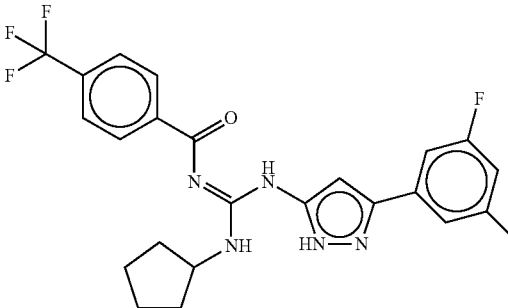
Compound No.	Chemical Structure	Calculated	MS (m/z)	HPLC Method	HPLC Retention
		MW (g/mol)			Time (min)
A-287		449.86	449.97, 472.00	B	5.84
A-288		475.89	497.99	B	7.42
A-289		461.87	461.99	B	5.89
A-290		449.86	472	B	7.31
A-291		477.43	478.04, 499.94	B	5.88

TABLE 2-continued

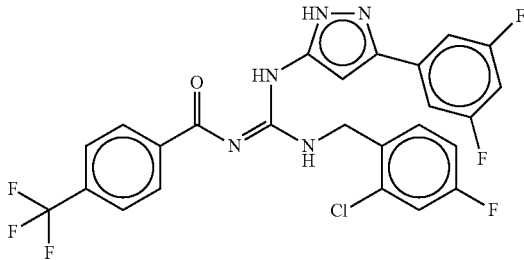
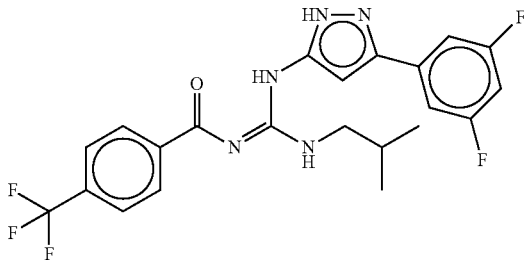
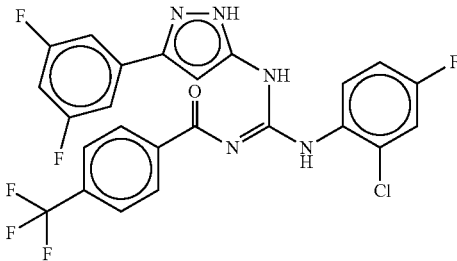
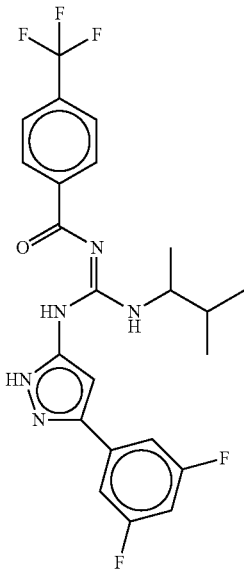
Compound No.	Chemical Structure	Calculated	MS (m/z)	HPLC Method	HPLC
		MW (g/mol)			Retention Time (min)
A-292		551.87	551.94, 553.89	B	7.06
A-293		465.42	466.02, 487.92	B	5.83
A-294		537.84	NA	NA	NA
A-295		479.45	NA	NA	NA

TABLE 2-continued

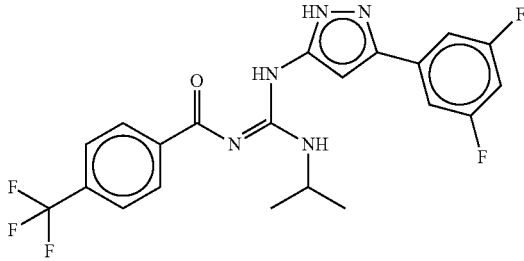
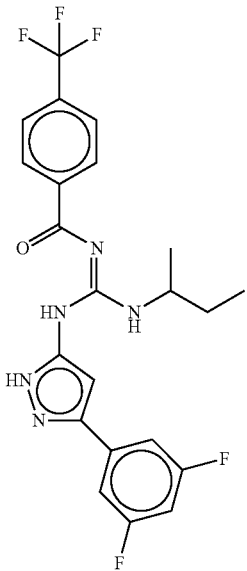
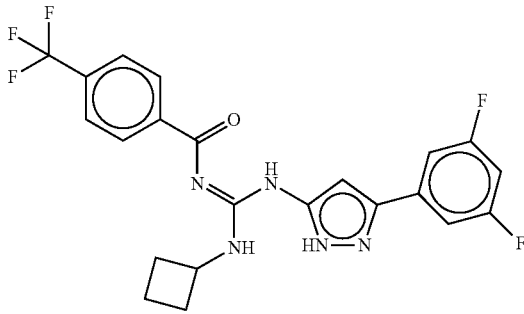
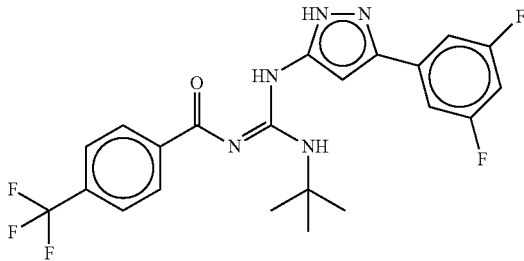
Compound No.	Chemical Structure	Calculated	MS (m/z)	HPLC Method	HPLC Retention
		MW (g/mol)			Time (min)
A-296		451.39	451.98, 473.95	B	5.6
A-297		465.42	466.02, 487.98	B	5.86
A-298		463.4	464.00, 485.90	B	5.75
A-299		465.42	465.95, 487.98	B	7.21

TABLE 2-continued

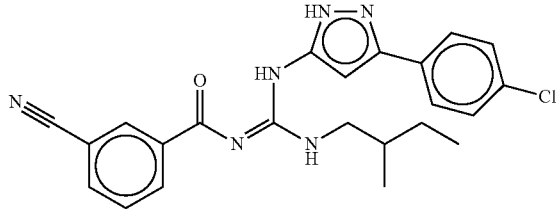
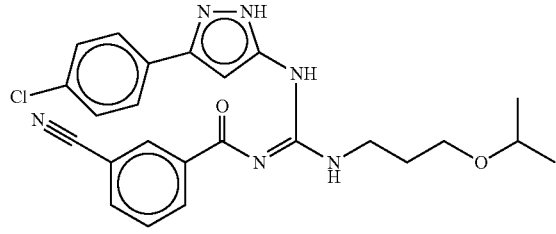
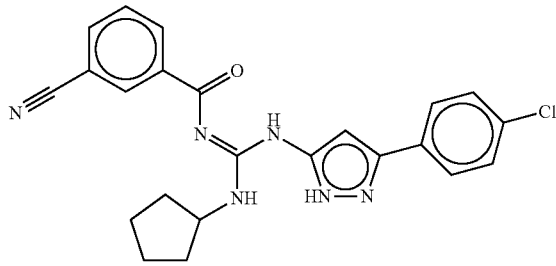
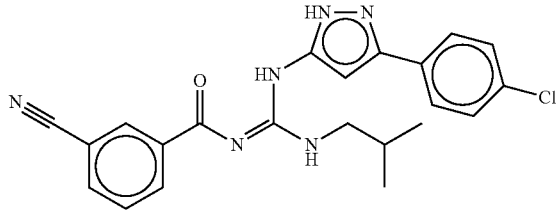
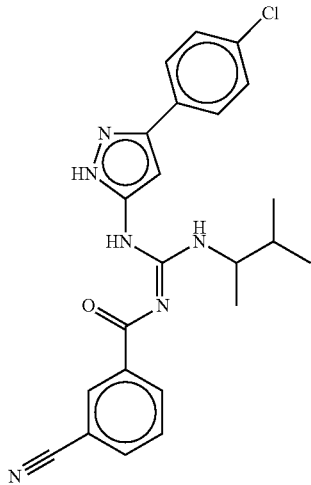
Compound No.	Chemical Structure	Calculated MW (g/mol)	MS (m/z)	HPLC Method	HPLC Retention Time (min)
A-300		434.92	434.96	B	5.8
A-301		464.95	464.98	B	5.44
A-302		432.91	433.01, 454.97	B	5.55
A-303		420.89	420.99, 442.95	B	5.5
A-304		434.92	435.02, 456.99	B	5.83

TABLE 2-continued

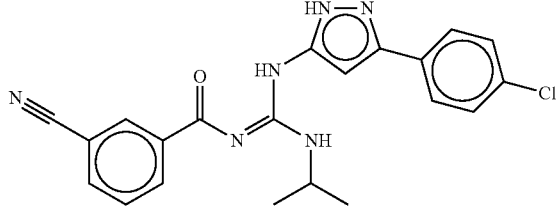
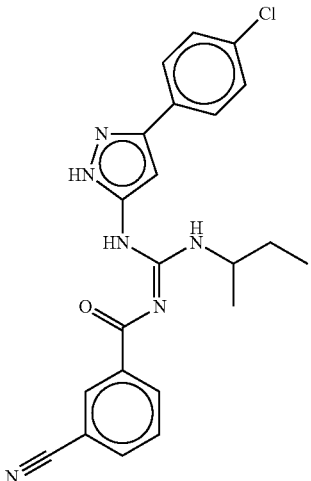
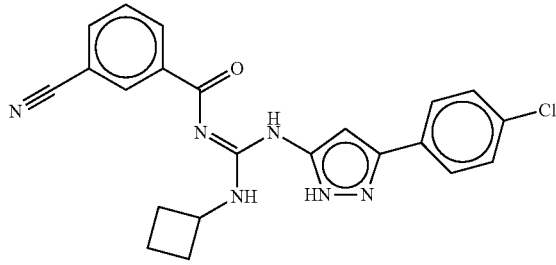
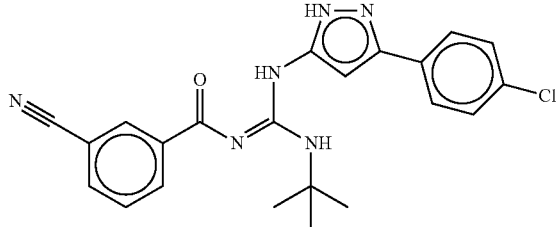
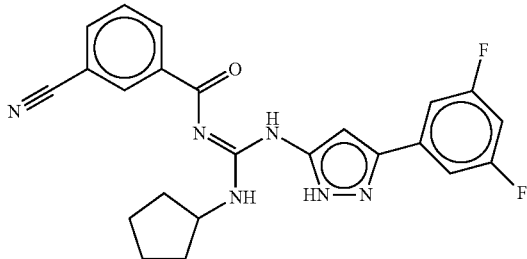
Compound No.	Chemical Structure	Calculated MW (g/mol)	MS (m/z)	HPLC Method	HPLC Retention Time (min)
A-305		406.87	406.95, 428.91	B	5.24
A-306		420.89	420.99, 442.95	B	5.53
A-307		418.88	418.97, 440.94	B	5.42
A-308		420.89	420.99, 442.95	B	6.85
A-309		434.44	434.96, 456.99	B	5.51

TABLE 2-continued

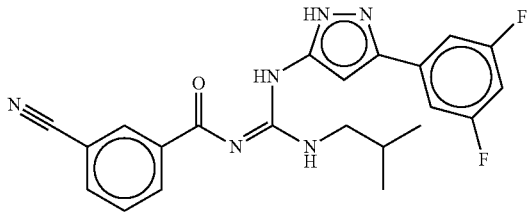
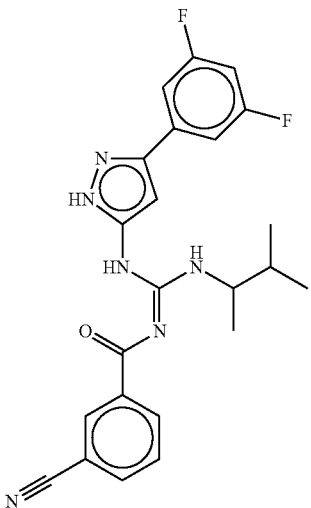
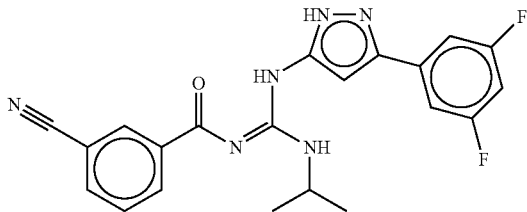
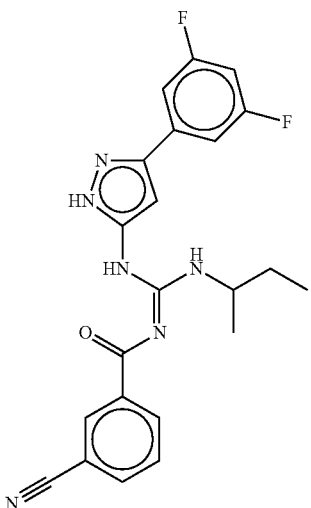
Compound No.	Chemical Structure	Calculated MW (g/mol)	MS (m/z)	HPLC Method	HPLC Retention Time (min)
A-310		422.43	423.00, 444.96	B	5.46
A-311		436.46	436.96, 459.00	B	5.61
A-312		408.4	NA	NA	NA
A-313		422.43	423.00, 444.96	B	6.51

TABLE 2-continued

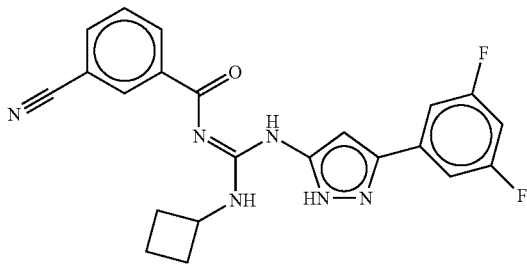
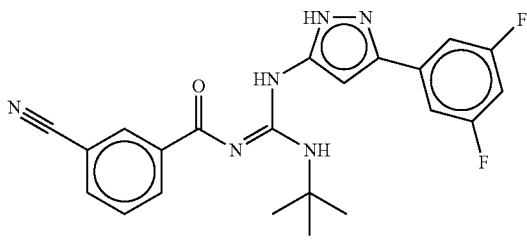
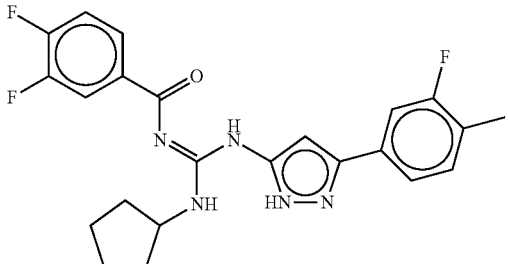
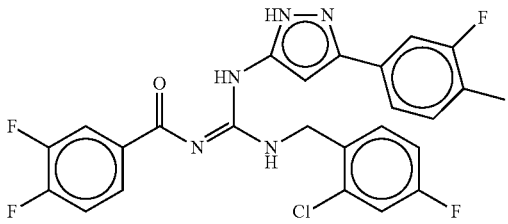
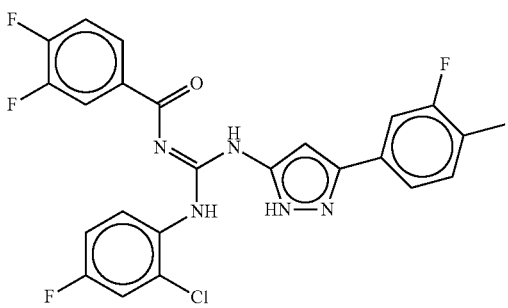
Compound No.	Chemical Structure	Calculated	MS	HPLC	HPLC
		MW (g/mol)	(m/z)	Method	Retention Time (min)
A-314		420.41	420.99, 442.95	B	5.37
A-315		422.43	NA	NA	NA
A-316		441.45	NA	NA	NA
A-317		515.89	NA	NA	NA
A-318		501.86	NA	NA	NA



TABLE 2-continued

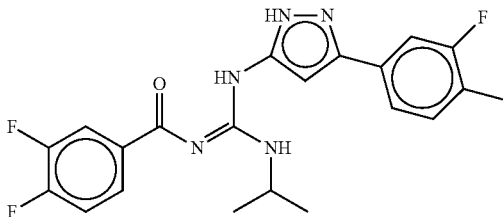
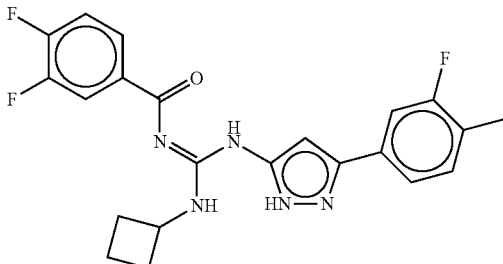
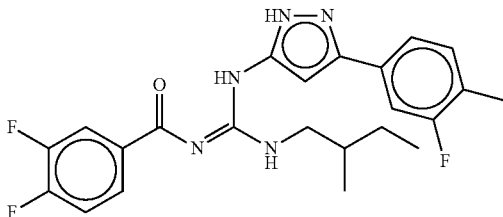
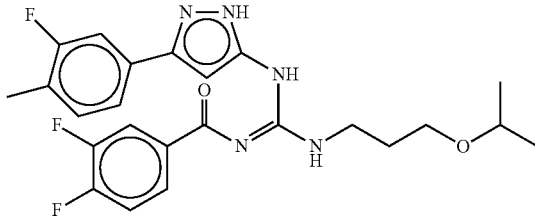
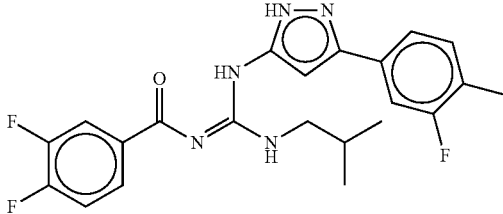
Compound No.	Chemical Structure	Calculated	MS	HPLC	HPLC
		MW (g/mol)	(m/z)	Method	Retention Time (min)
A-319		415.41	NA	B	5.42
A-320		427.42	NA	NA	NA
A-321		443.46	NA	NA	NA
A-322		473.49	NA	NA	NA
A-323		429.44	NA	B	5.65

TABLE 2-continued

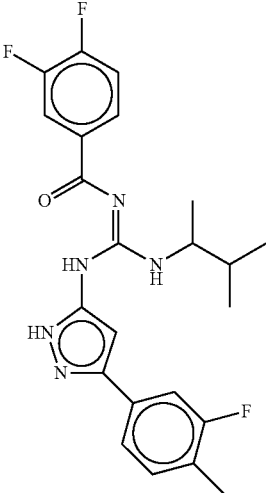
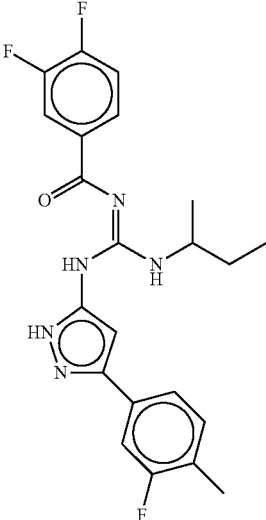
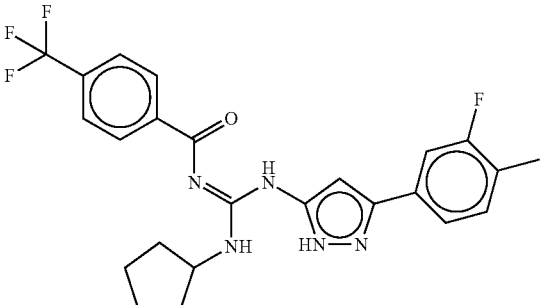
Compound No.	Chemical Structure	Calculated	MS (m/z)	HPLC Method	HPLC
		MW (g/mol)			Retention Time (min)
A-324		443.46	NA	NA	NA
A-325		429.44	NA	NA	NA
A-326		473.47	NA	NA	NA

TABLE 2-continued

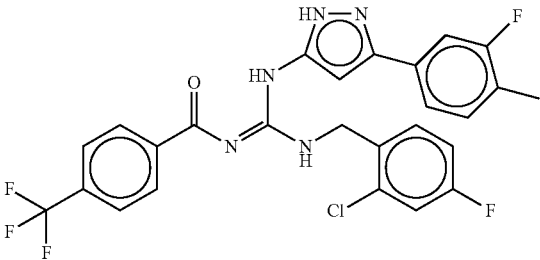
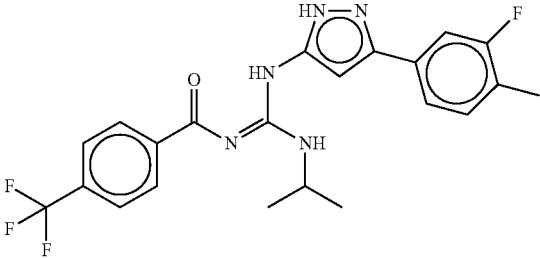
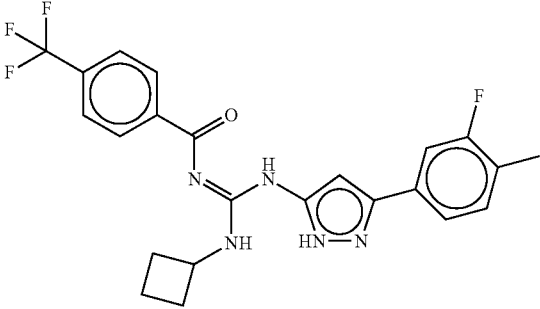
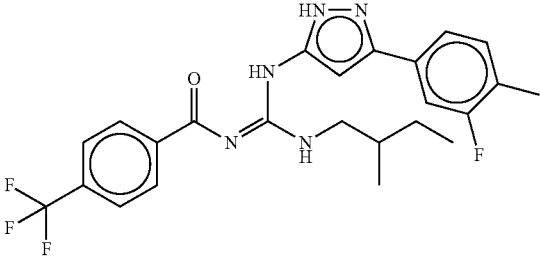
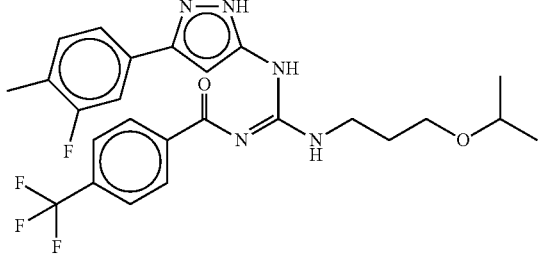
Compound No.	Chemical Structure	Calculated	MS	HPLC	HPLC
		MW (g/mol)	(m/z)	Method	Retention Time (min)
A-327		547.91	NA	NA	NA
A-328		447.43	NA	NA	NA
A-329		459.44	NA	NA	NA
A-330		475.48	NA	NA	NA
A-331		505.51	NA	NA	NA

TABLE 2-continued

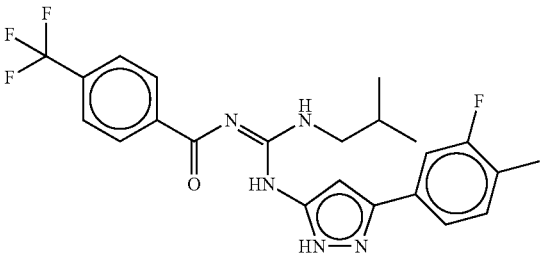
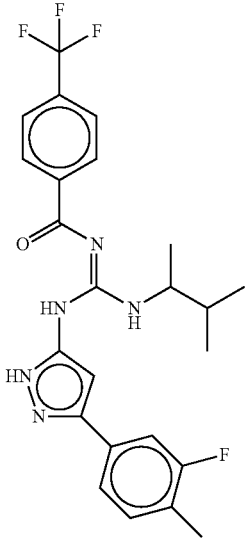
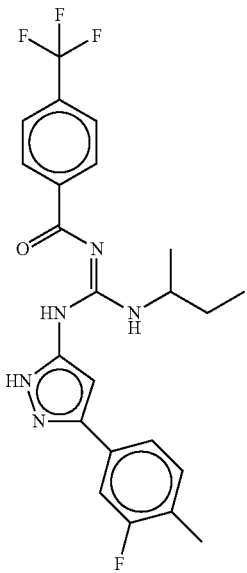
Compound No.	Chemical Structure	Calculated	MS	HPLC	HPLC
		MW (g/mol)	(m/z)	Method	Retention Time (min)
A-332		461.46	NA	NA	NA
A-333		475.48	NA	NA	NA
A-334		461.46	NA	NA	NA

TABLE 2-continued

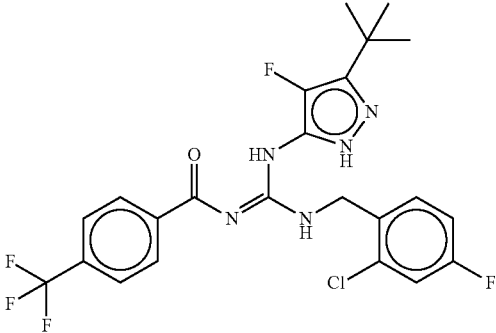
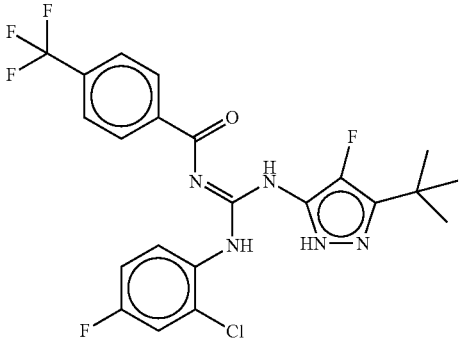
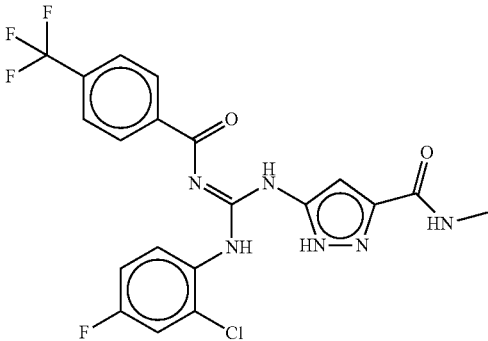
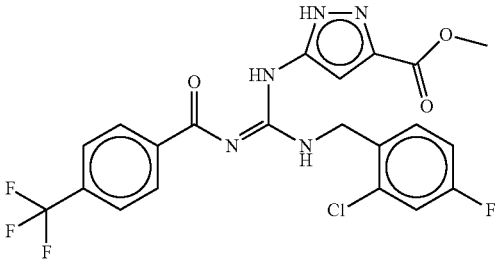
Compound No.	Chemical Structure	Calculated	MS (m/z)	HPLC Method	HPLC Retention
		MW (g/mol)			Time (min)
A-335		513.89	513.91, 535.88	B	7.64
A-336		499.86	NA	NA	NA
A-337		482.82	NA	NA	NA
A-338		497.83	497.86, 519.83	B	6.47

TABLE 2-continued

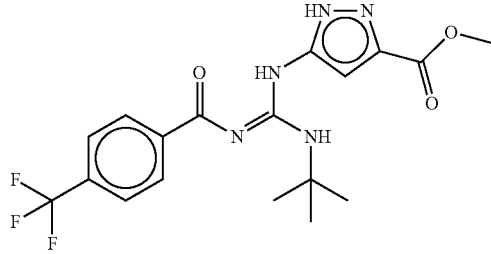
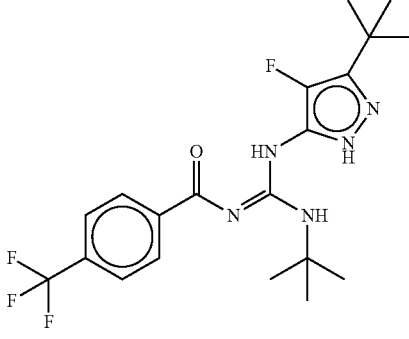
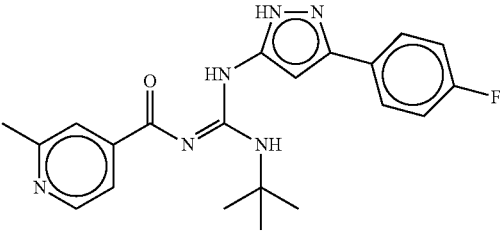
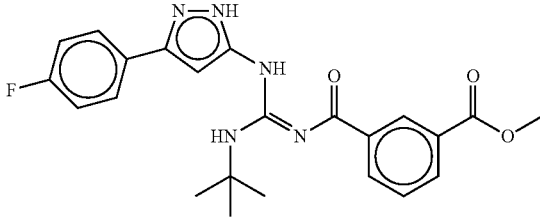
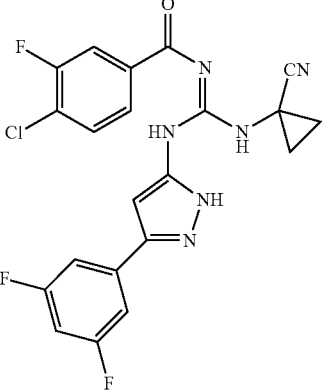
Compound No.	Chemical Structure	Calculated MW (g/mol)	MS (m/z)	HPLC Method	HPLC Retention Time (min)
A-339		411.38	433.98	B	6.47
A-340		427.44	428.00, 450.10	B	7.67
A-341		394.45	NA	NA	NA
A-342		437.47	NA	NA	NA
A-343		458.82	NA	NA	NA

TABLE 2-continued

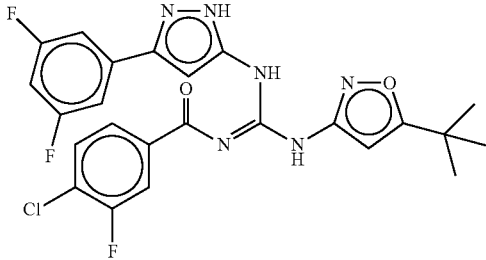
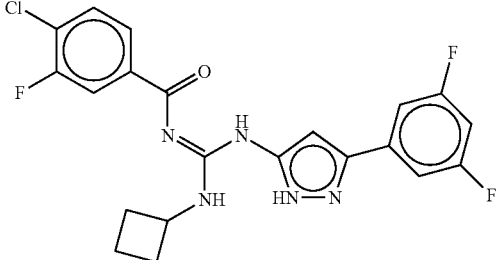
Compound No.	Chemical Structure	Calculated	MS (m/z)	HPLC Method	HPLC
		MW (g/mol)			Retention Time (min)
A-344		493.91	NA	NA	NA
A-345		516.9	NA	NA	NA
A-346		463.88	463.94	B	6.29
A-347		447.84	447.95, 469.92	B	5.9

TABLE 2-continued

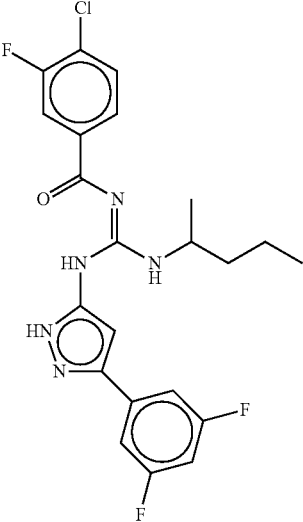
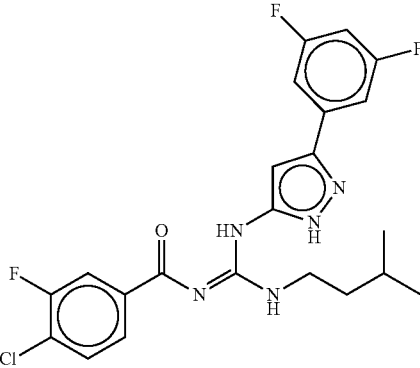
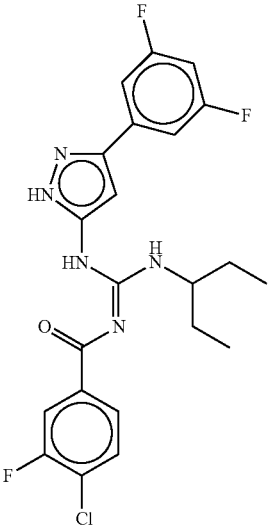
Compound No.	Chemical Structure	Calculated	MS (m/z)	HPLC	
		MW (g/mol)		HPLC Method	Retention Time (min)
A-348		463.88	NA	NA	NA
A-349		463.88	NA	NA	NA
A-350		463.88	NA	NA	NA



TABLE 2-continued

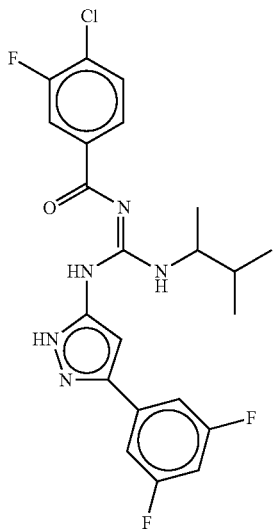
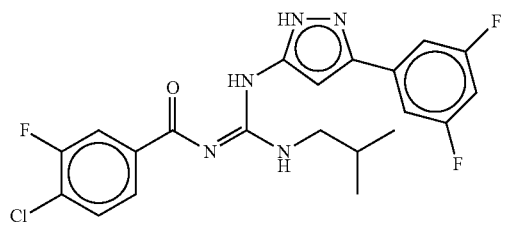
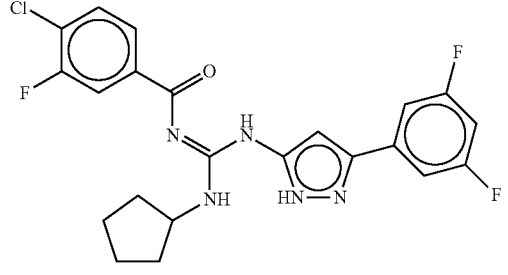
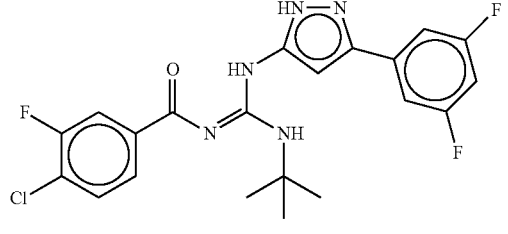
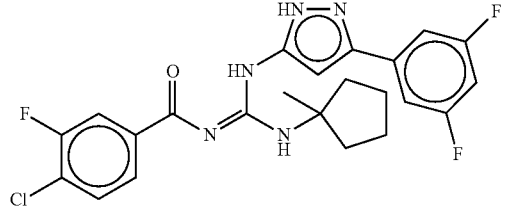
Compound No.	Chemical Structure	Calculated MW (g/mol)	MS (m/z)	HPLC Method	HPLC Retention Time (min)
A-351		463.88	464.00, 485.97	B	6.33
A-352		449.86	449.90, 471.87	B	5.98
A-353		461.87	NA	NA	NA
A-354		449.86	NA	NA	NA
A-355		475.89	NA	NA	NA

TABLE 2-continued

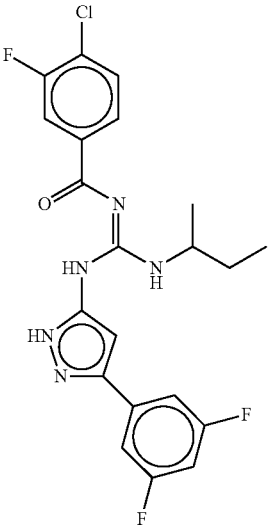
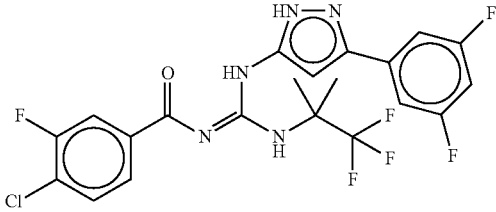
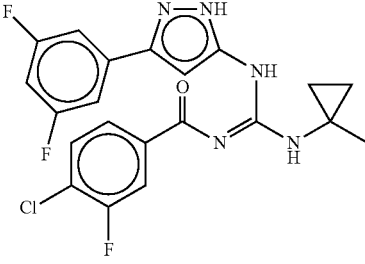
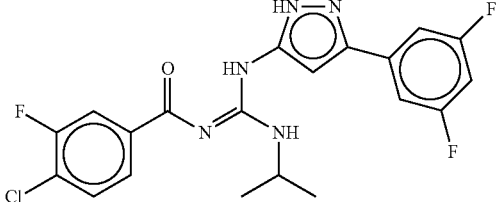
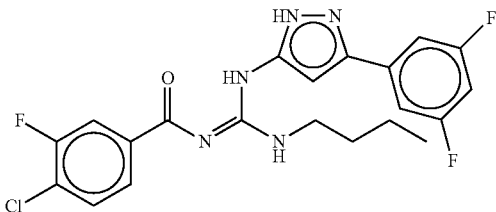
Compound No.	Chemical Structure	Calculated MW (g/mol)	MS (m/z)	HPLC Method	HPLC Retention Time (min)
A-356		449.86	449.90, 471.93	B	6.03
A-357		503.83	NA	NA	NA
A-358		447.84	NA	NA	NA
A-359		435.83	NA	NA	NA
A-360		449.86	NA	NA	NA

TABLE 2-continued

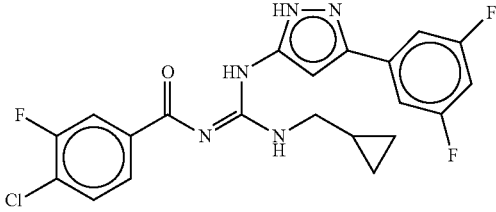
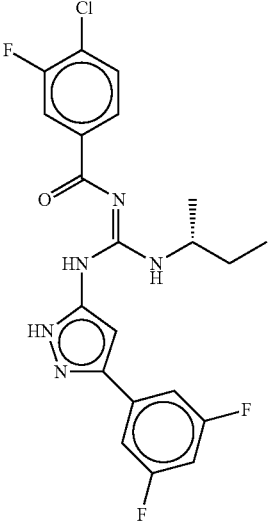
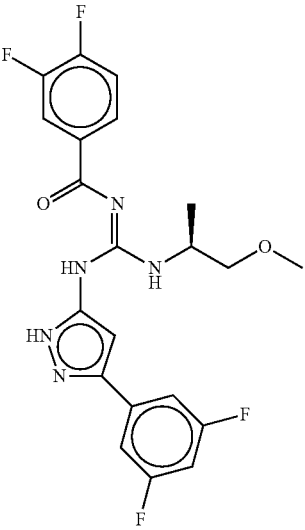
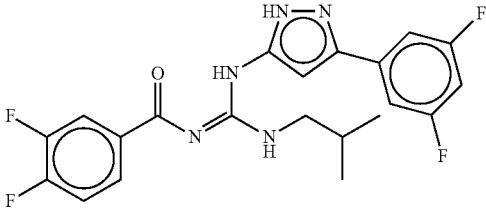
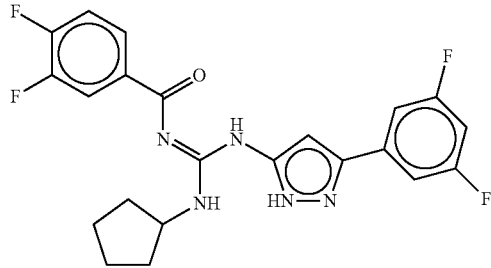
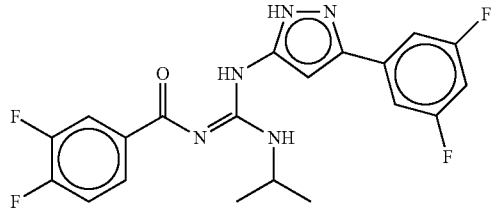
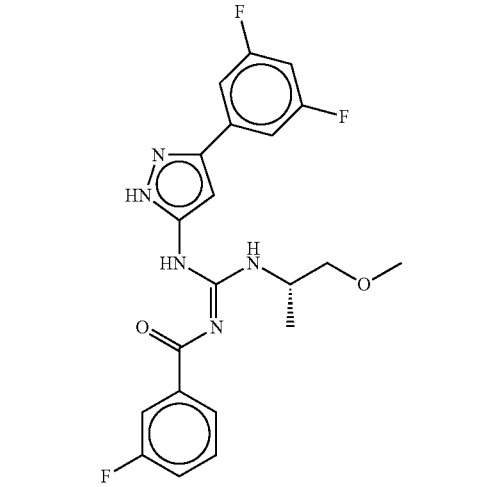
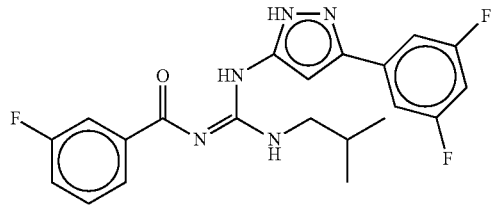
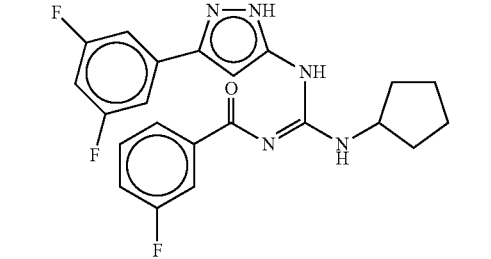
Compound No.	Chemical Structure	Calculated MW (g/mol)	MS (m/z)	HPLC Method	HPLC Retention Time (min)
A-361		447.84	NA	NA	NA
A-362		449.86	449.90, 471.87	B	5.83
A-363		449.4	449.90, 471.87	B	5.2
A-364		433.4	433.92, 455.88	B	5.39

TABLE 2-continued

Compound No.	Chemical Structure	Calculated MW (g/mol)	MS (m/z)	HPLC Method	HPLC Retention Time (min)
A-365		445.41	445.87, 467.87	B	5.45
A-366		419.38	419.88, 441.91	B	5.14
A-367		431.41	NA	NA	NA
A-368		415.41	NA	NA	NA
A-369		427.42	427.94, 449.90	B	5.2

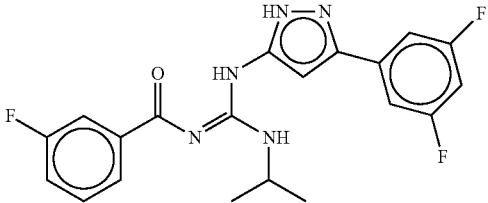
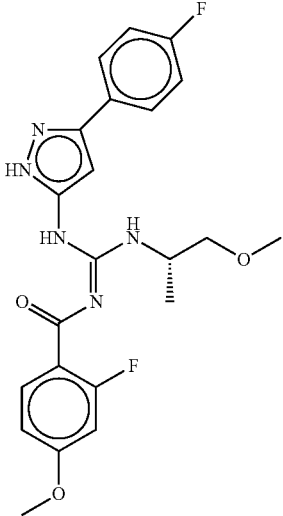
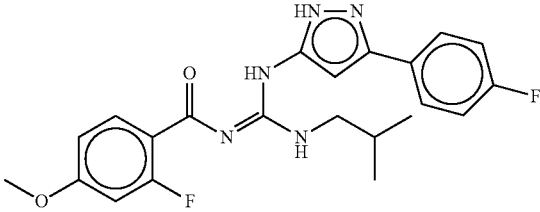
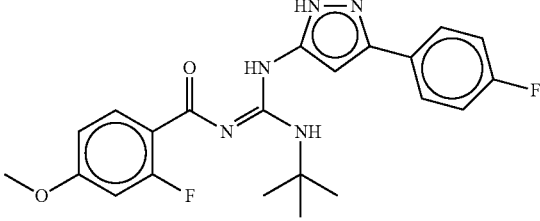
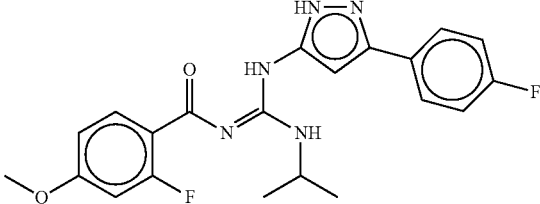
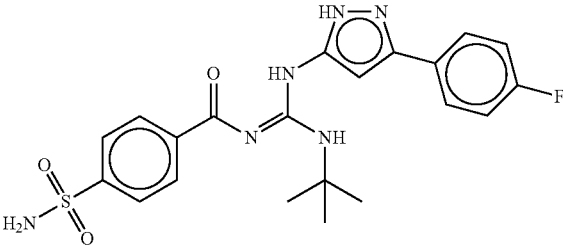
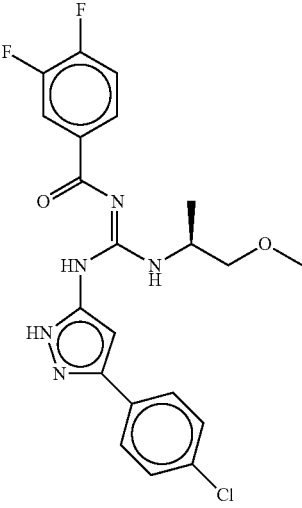
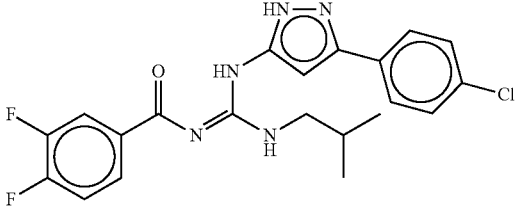
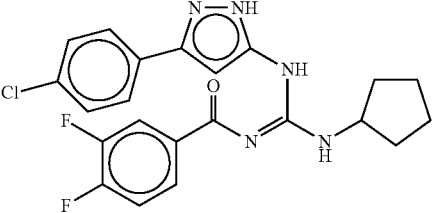
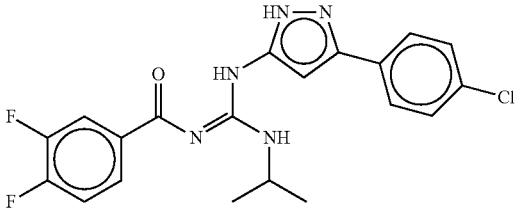
Compound No.	Chemical Structure	Calculated MW (g/mol)	MS (m/z)	HPLC Method	HPLC Retention Time (min)
A-370		401.39	401.95, 423.98	B	4.84
A-371		443.45	NA	NA	NA
A-372		427.45	NA	NA	NA
A-373		427.45	NA	NA	NA
A-374		413.42	NA	NA	NA

TABLE 2-continued

Compound No.	Chemical Structure	Calculated MW (g/mol)	MS (m/z)	HPLC Method	HPLC Retention Time (min)
A-375		458.51	457.9	B	5.13
A-376		447.87	447.95	B	5.4
A-377		431.87	431.9	B	5.62
A-378		443.88	443.92	B	5.68
A-379		417.84	417.87	B	5.37

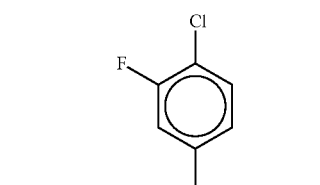
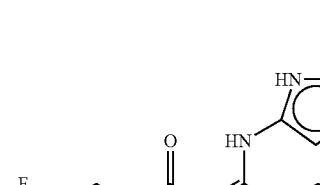

Compound No.	Chemical Structure	Calculated		HPLC	HPLC
		MW (g/mol)	MS (m/z)	Method	Retention Time (min)
A-380		464.32	463.87, 465.82	B	5.79
A-381		448.32	447.89, 449.84	B	5.99
A-382		460.33	459.85, 461.86	B	6.05
A-383		434.29	433.85, 435.87	B	5.74

TABLE 2-continued

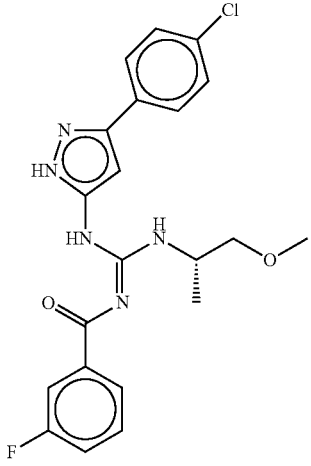
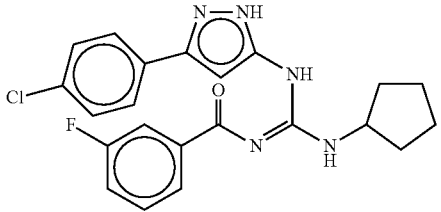
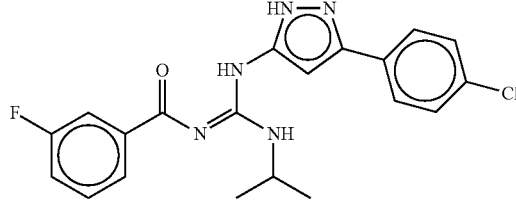
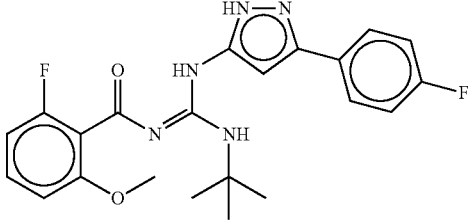
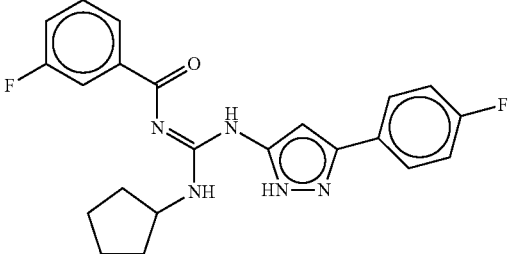
Compound No.	Chemical Structure	Calculated	MS (m/z)	HPLC Method	HPLC Retention
		MW (g/mol)			Time (min)
A-384		429.88	NA	NA	NA
A-385		425.89	425.93, 427.87	B	5.45
A-386		399.85	399.93, 401.88	B	5.04
A-387		427.45	NA	NA	NA
A-388		409.43	NA	NA	NA



TABLE 2-continued

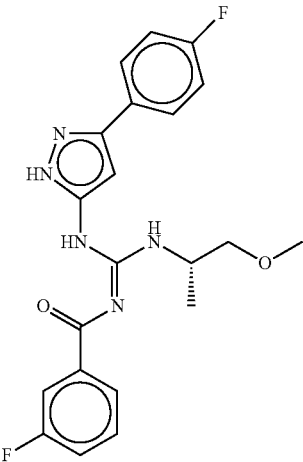
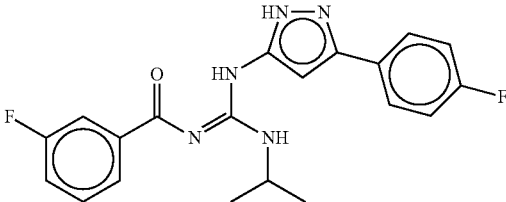
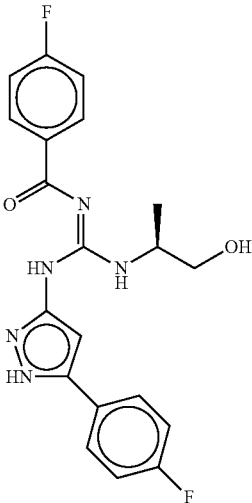
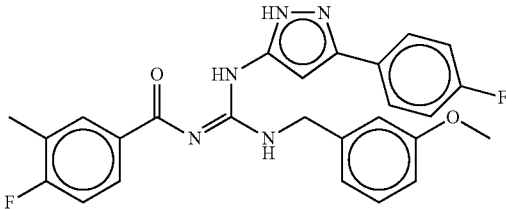
Compound No.	Chemical Structure	Calculated	MS (m/z)	HPLC Method	HPLC
		MW (g/mol)			Retention Time (min)
A-389		413.42	NA	NA	NA
A-390		383.39	NA	NA	NA
A-391		399.39	NA	NA	NA
A-392		475.49	NA	NA	NA

TABLE 2-continued

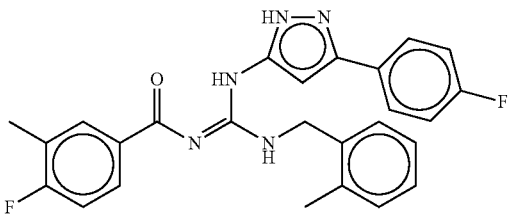
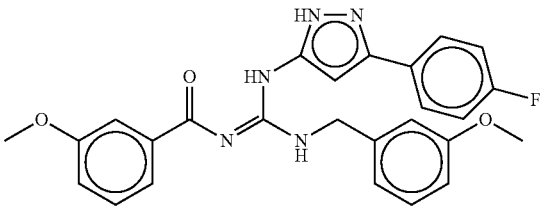
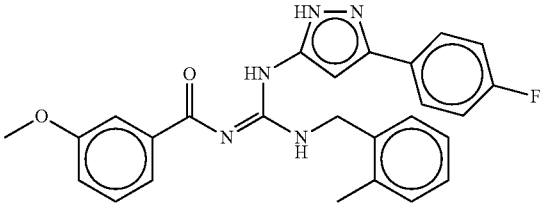
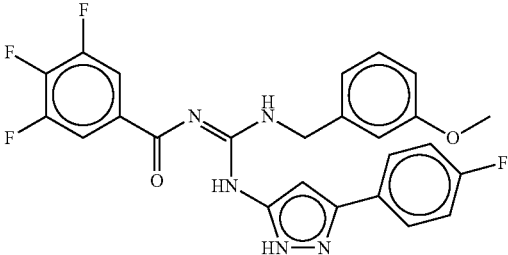
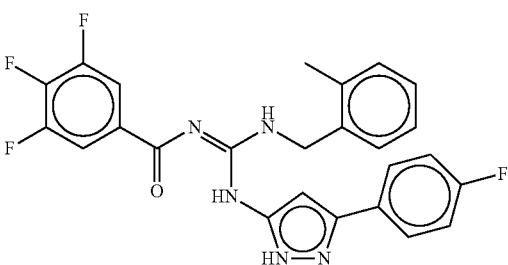
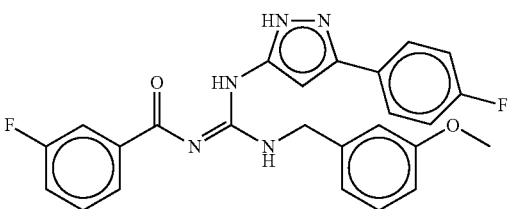
Compound No.	Chemical Structure	Calculated MW (g/mol)	MS (m/z)	HPLC Method	HPLC Retention Time (min)
A-393		459.49	NA	NA	NA
A-394		473.5	NA	NA	NA
A-395		457.5	NA	NA	NA
A-396		497.44	497.86	B	6.71
A-397		481.45	NA	NA	NA
A-398		461.46	461.92	B	5.39

TABLE 2-continued

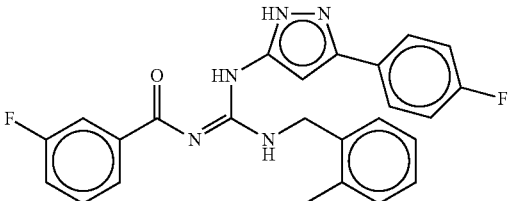
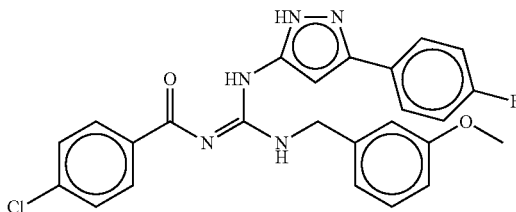
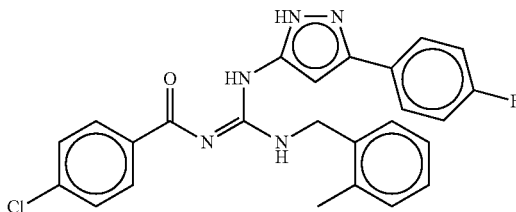
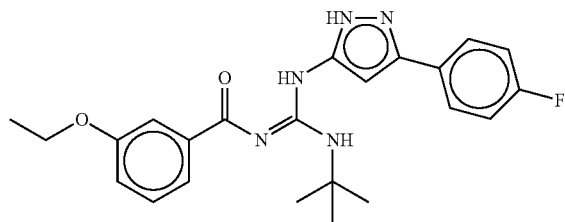
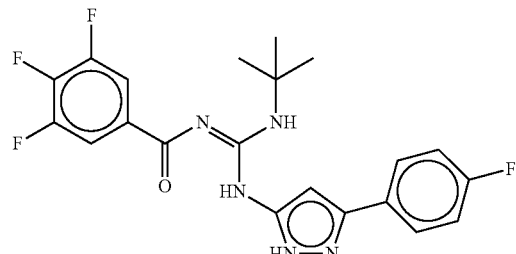
Compound No.	Chemical Structure	Calculated	MS	HPLC	HPLC
		MW (g/mol)	(m/z)	Method	Retention Time (min)
A-399		445.46	445.94	B	5.55
A-400		477.92	NA	NA	NA
A-401		461.92	NA	NA	NA
A-402		423.48	NA	NA	NA
A-403		433.4	455.95	B	7.43

TABLE 2-continued

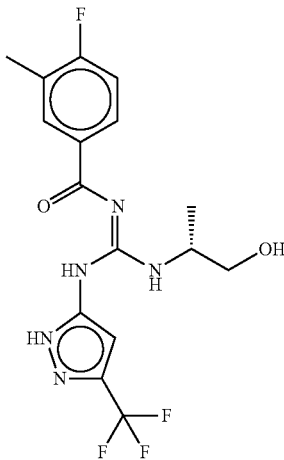
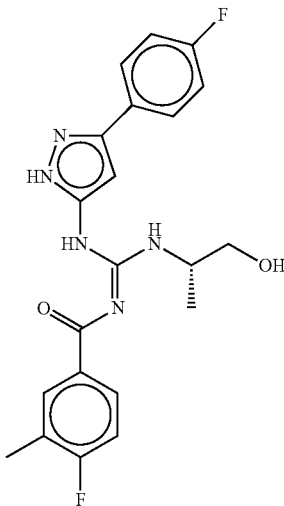
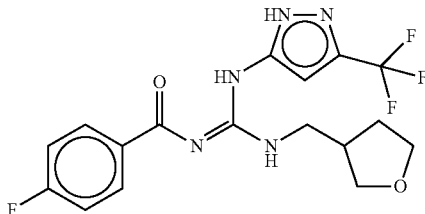
Compound No.	Chemical Structure	Calculated	MS (m/z)	HPLC Method	HPLC
		MW (g/mol)			Retention Time (min)
A-404		387.33	NA	NA	NA
A-405		413.42	NA	NA	NA
A-406		399.34	NA	NA	NA

TABLE 2-continued

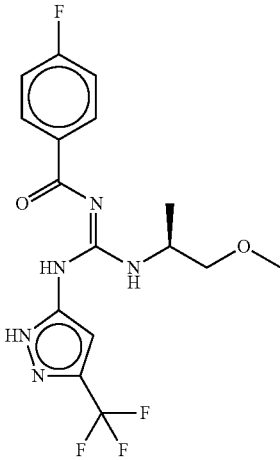
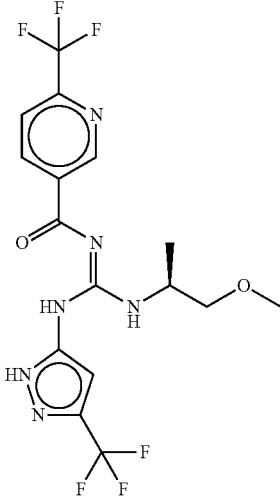
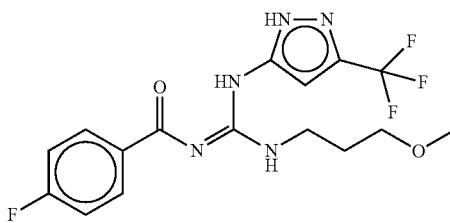
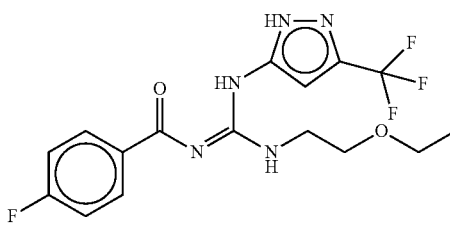
Compound No.	Chemical Structure	Calculated	MS (m/z)	HPLC Method	HPLC
		MW (g/mol)			Retention Time (min)
A-407		387.33	NA	NA	NA
A-408		438.33	NA	NA	NA
A-409		387.33	NA	NA	NA
A-410		387.33	NA	NA	NA

TABLE 2-continued

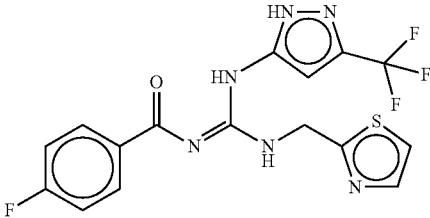
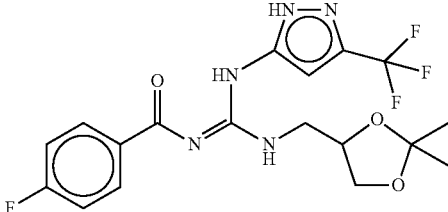
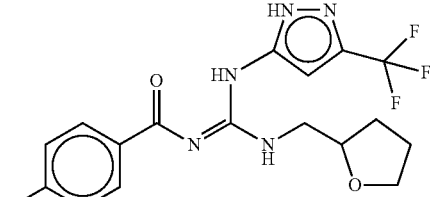
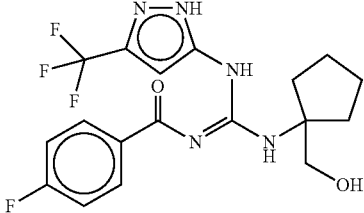
Compound No.	Chemical Structure	Calculated	MS (m/z)	HPLC Method	HPLC Retention
		MW (g/mol)			Time (min)
A-411		412.36	NA	NA	NA
A-412		429.37	NA	NA	NA
A-413		399.34	NA	NA	NA
A-414		409.34	431.9	B	8.27
A-415		413.37	NA	NA	NA
A-416		426.39	NA	NA	NA

TABLE 2-continued

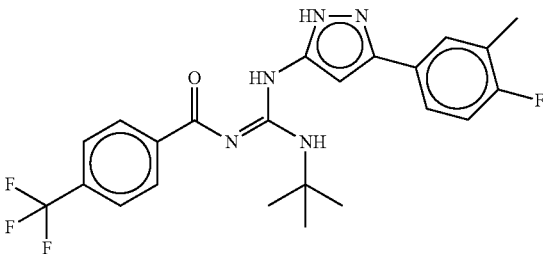
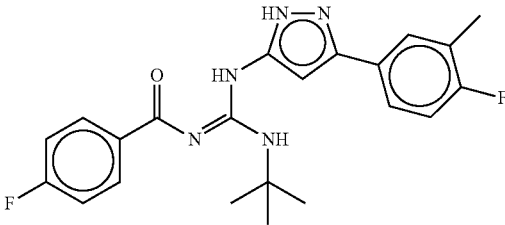
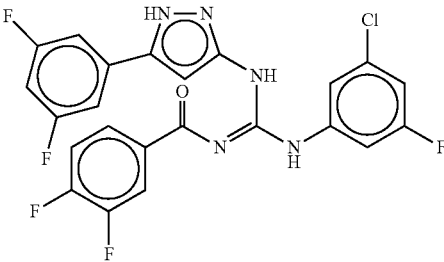
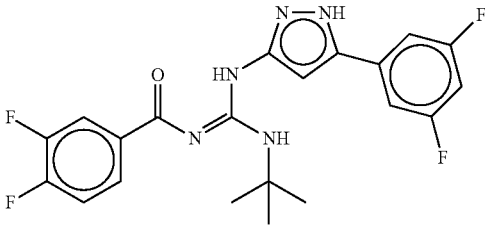
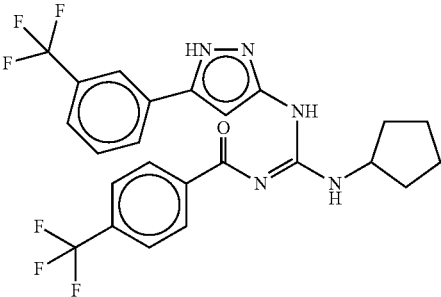
Compound No.	Chemical Structure	Calculated MW (g/mol)	MS (m/z)	HPLC Method	HPLC Retention Time (min)
A-417		461.46	NA	NA	NA
A-418		411.45	412.03, 434.01	A	9.71
A-419		505.83	505.94, 527.93	B	7.9
A-420		433.4	456.06	B	7.02
A-421		509.45	510.16	B	6.07

TABLE 2-continued

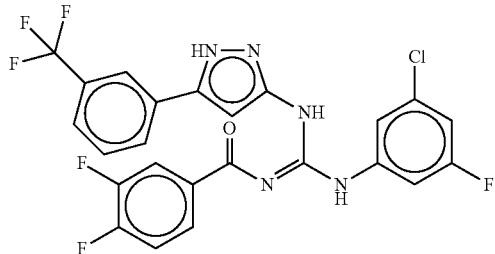
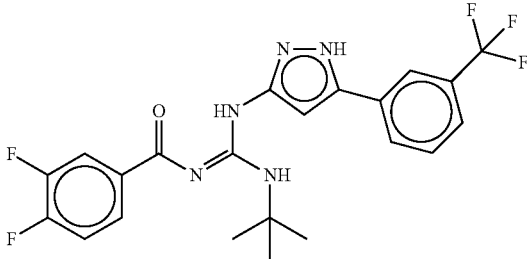
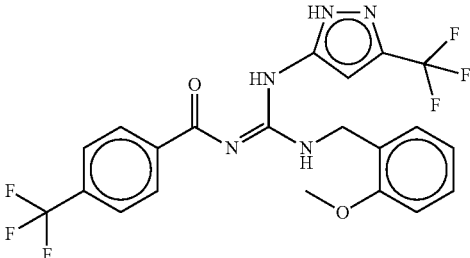
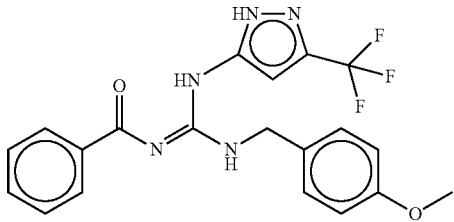
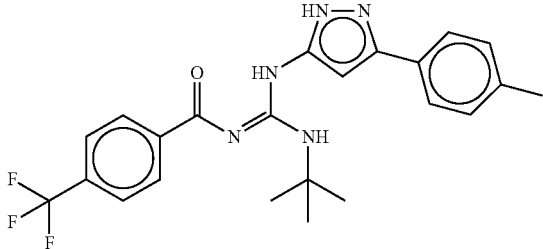
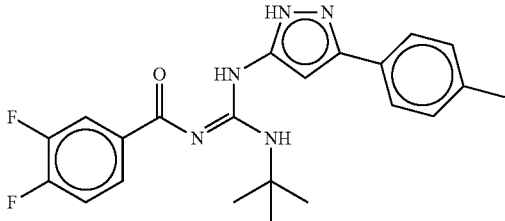
Compound No.	Chemical Structure	Calculated MW (g/mol)	MS (m/z)	HPLC Method	HPLC Retention Time (min)
A-422		537.84	538.01, 540.02	B	8.12
A-423		465.42	466.07, 488.05	B	7.2
A-424		485.38	486.5	D	2.5
A-425		417.38	418.5	D	2.05
A-426		443.46	444.4	D	2.77
A-427		411.45	412.3	D	2.64



TABLE 2-continued

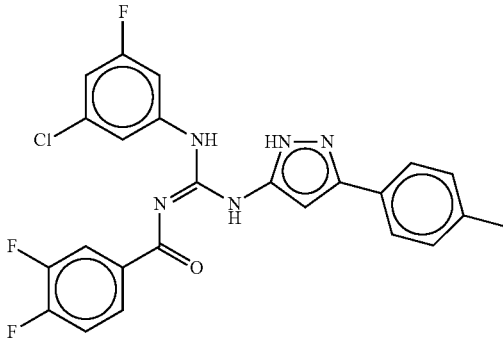
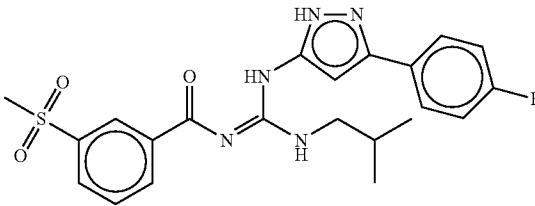
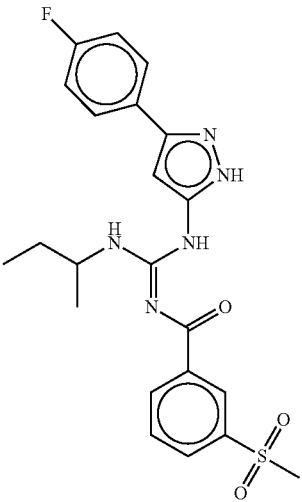
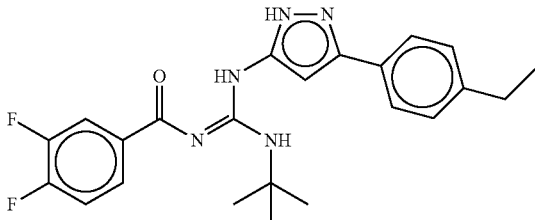
Compound No.	Chemical Structure	Calculated		HPLC	
		MW (g/mol)	MS (m/z)	HPLC Method	Retention Time (min)
A-428		483.87	484.3	D	3.22
A-429		457.52	NA	E	7.09
A-430		457.52	NA	E	7.2
A-431		425.47	426.1	D	2.82

TABLE 2-continued

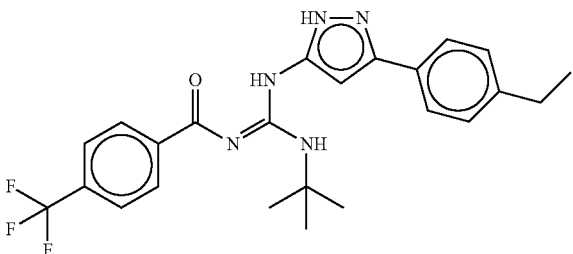
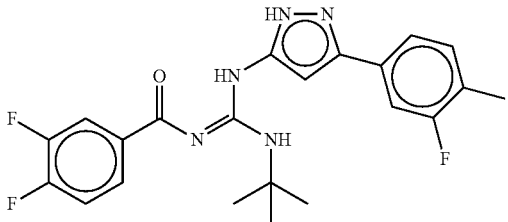
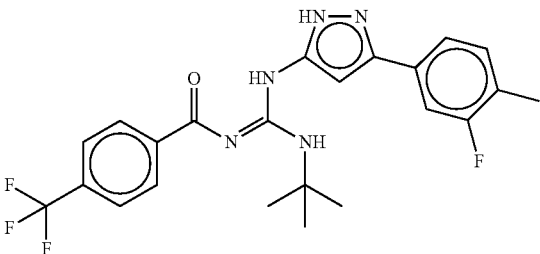
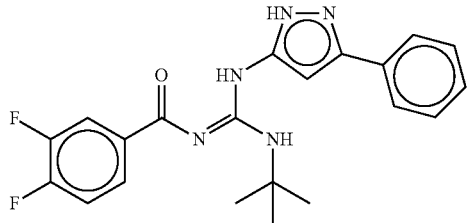
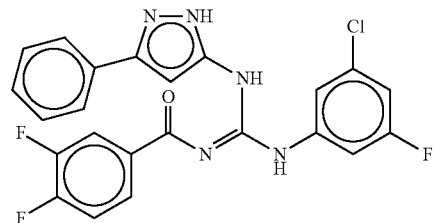
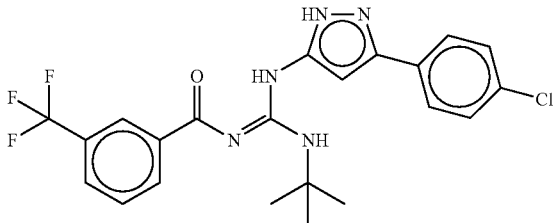
Compound No.	Chemical Structure	Calculated MW (g/mol)	MS (m/z)	HPLC Method	HPLC Retention Time (min)
A-432		457.49	458.5	D	2.94
A-433		429.44	430.3	D	2.73
A-434		461.46	462.1	D	2.85
A-435		397.42	398.2	D	2.58
A-436		469.85	490.2	D	3.13
A-437		463.88	464	D	3.04

TABLE 2-continued

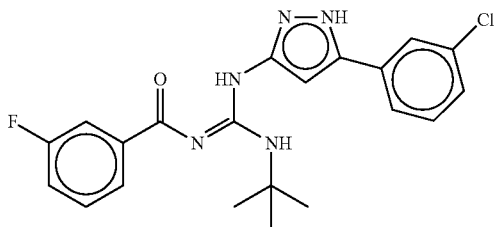
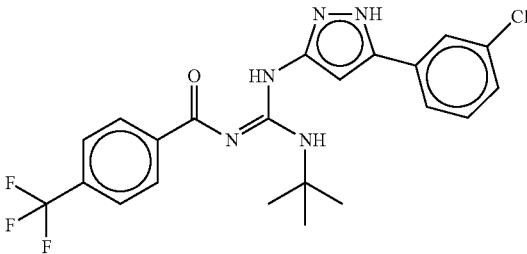
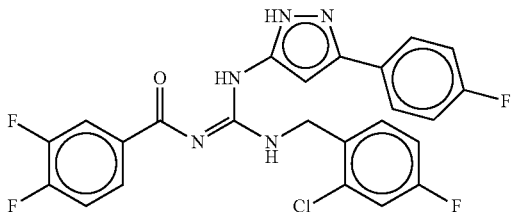
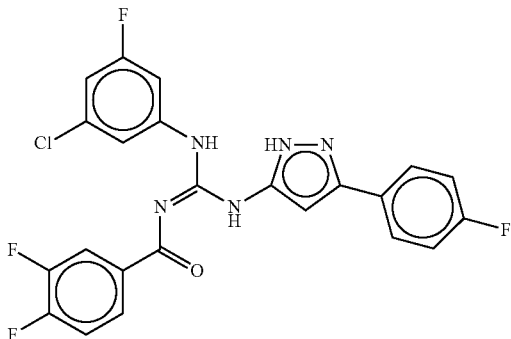
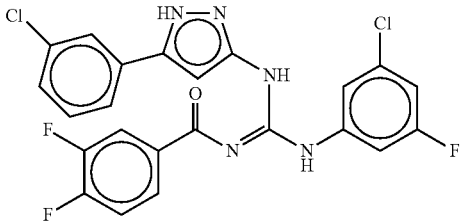
Compound No.	Chemical Structure	Calculated MW (g/mol)	MS (m/z)	HPLC Method	HPLC Retention Time (min)
A-438		413.88	414	D	2.64
A-439		463.88	464	D	3.01
A-440		501.86	502	D	2.73
A-441		487.84	488	D	3.25
A-442		504.29	504	D	3.42

TABLE 2-continued

Compound No.	Chemical Structure	Calculated	MS (m/z)	HPLC Method	HPLC Retention
		MW (g/mol)			Time (min)
A-443		533.88	534	D	2.85
A-444		550.34	550.5	D	3.02
A-445		550.34	550.5	D	3
A-446		536.31	536	D	3.53
A-447		536.31	536	D	3.5

TABLE 2-continued

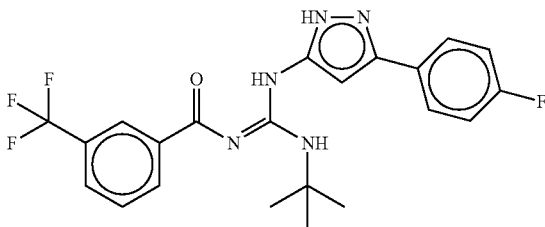
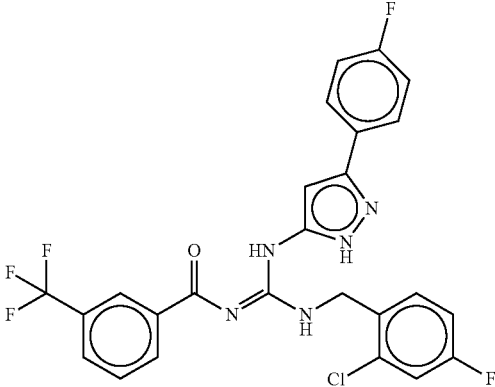
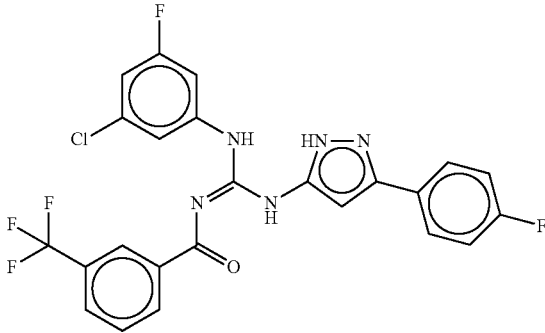
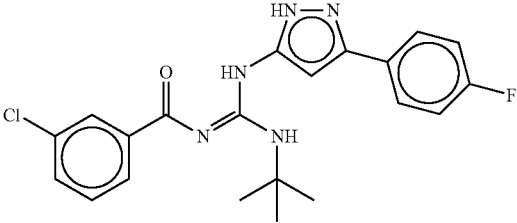
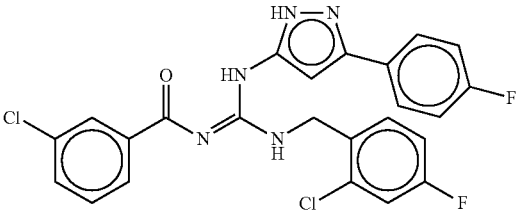
Compound No.	Chemical Structure	Calculated MW (g/mol)	MS (m/z)	HPLC Method	HPLC Retention Time (min)
A-448		447.43	448	D	2.77
A-449		533.88	534	D	2.79
A-450		519.85	520.5	D	3.22
A-451		413.88	414	D	2.58
A-452		500.33	500	D	2.62

TABLE 2-continued

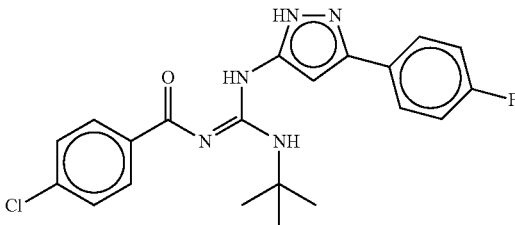
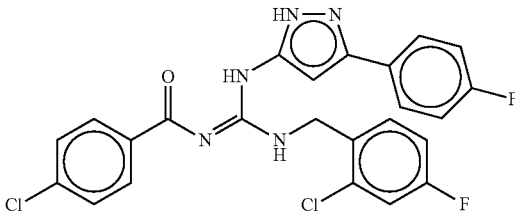
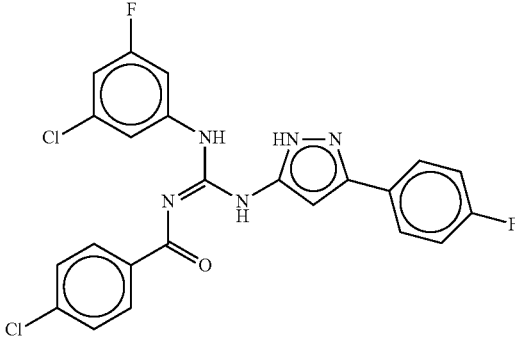
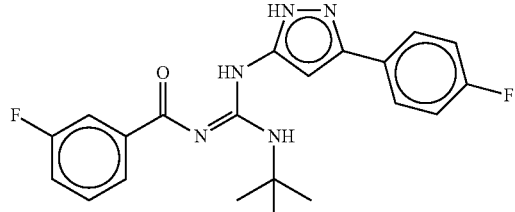
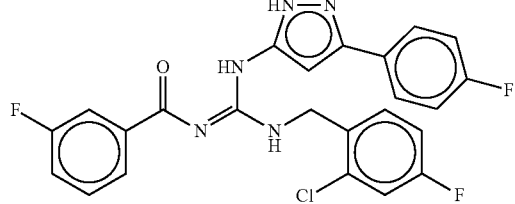
Compound No.	Chemical Structure	Calculated	MS	HPLC	HPLC
		MW (g/mol)	(m/z)	Method	Retention Time (min)
A-453		413.88	414.5	D	2.45
A-454		500.33	500	D	2.55
A-455		486.3	486.5	D	3.06
A-456		397.42	389	D	2.37
A-457		483.87	484.5	D	2.48

TABLE 2-continued

Compound No.	Chemical Structure	Calculated	MS (m/z)	HPLC Method	HPLC Retention
		MW (g/mol)			Time (min)
A-458		469.85	470.5	D	2.97
A-459		397.42	NA	D	2.24
A-460		483.87	484	D	2.36
A-461		469.85	470.5	D	2.87
A-462		471.91	472.5	D	2.21

TABLE 2-continued

Compound No.	Chemical Structure	Calculated	MS (m/z)	HPLC Method	HPLC Retention
		MW (g/mol)			Time (min)
A-463		476.33	476	D	2.33
A-464		476.33	476	D	2.31
A-465		475.44	476	D	2.11
A-466		457.45	458.5	D	2.08
A-467		443.9	444.5	D	2.68



TABLE 2-continued

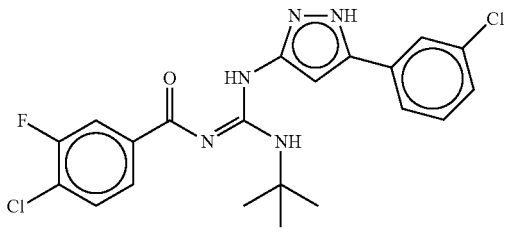
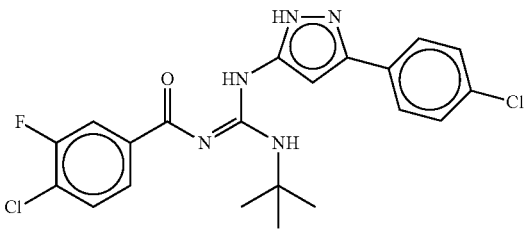
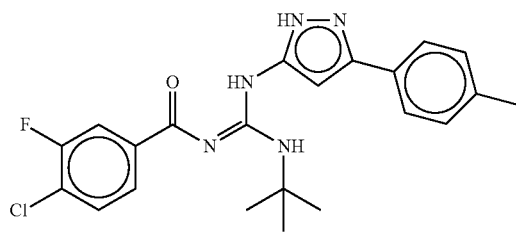
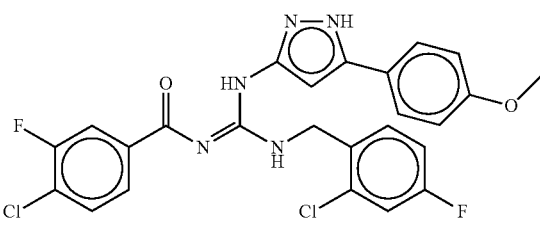
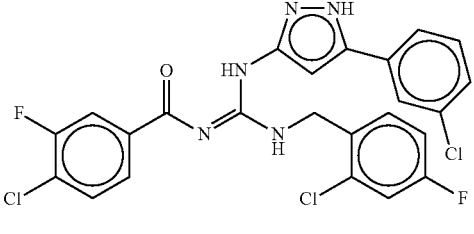
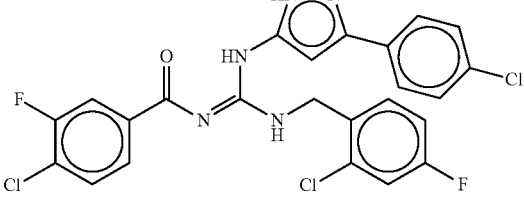
Compound No.	Chemical Structure	Calculated	MS (m/z)	HPLC Method	HPLC
		MW (g/mol)			Retention Time (min)
A-468		448.32	448	D	2.91
A-469		448.32	448	D	2.91
A-470		427.9	428	D	2.82
A-471		530.35	530	D	2.82
A-472		534.77	536	D	2.92
A-473		534.77	536	D	2.9

TABLE 2-continued

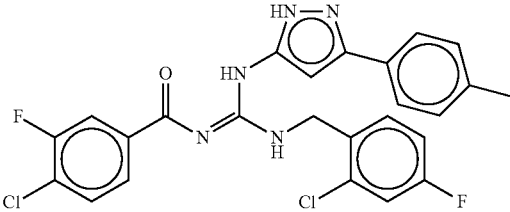
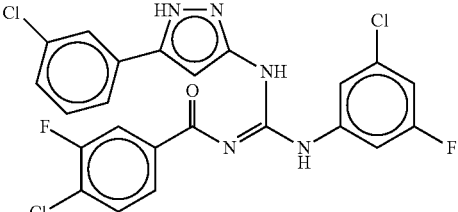
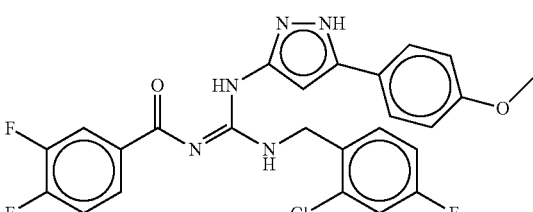
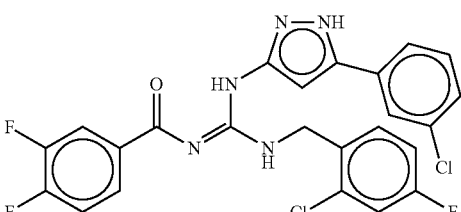
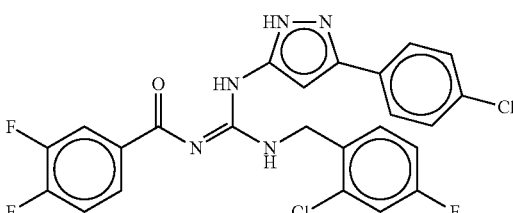
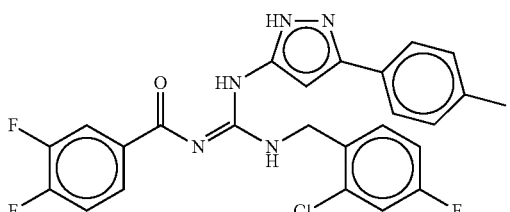
Compound No.	Chemical Structure	Calculated	MS (m/z)	HPLC Method	HPLC
		MW (g/mol)			Retention Time (min)
A-474		514.35	514.5	D	2.83
A-475		520.75	522	D	3.39
A-476		513.9	514.5	D	2.54
A-477		518.32	518	D	2.78
A-478		518.32	518	D	2.8
A-479		497.9	498.5	D	2.65

TABLE 2-continued

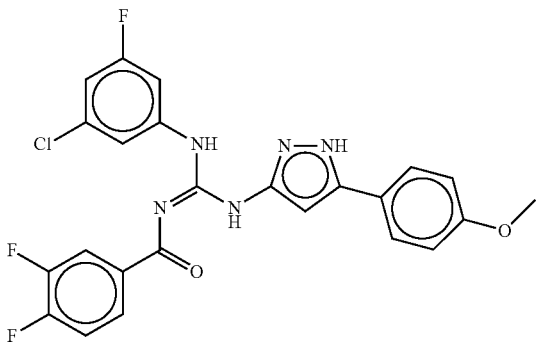
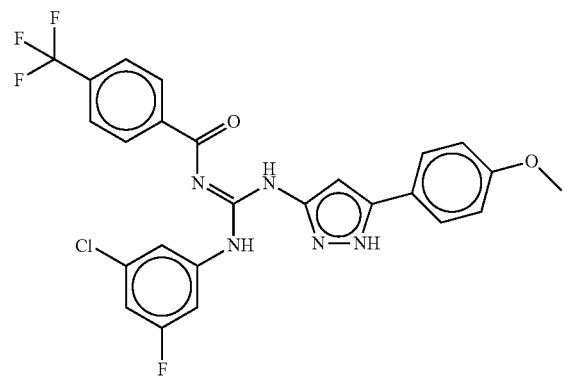
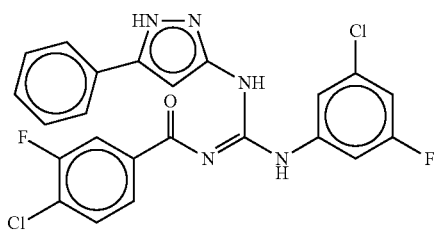
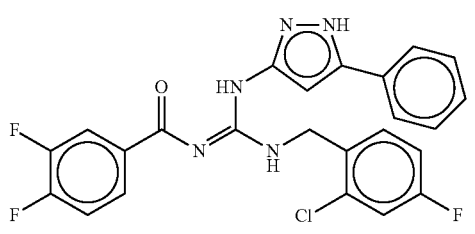
Compound No.	Chemical Structure	Calculated	MS	HPLC	HPLC
		MW (g/mol)	(m/z)	Method	Retention Time (min)
A-480		499.87	500	D	3.03
A-481		531.89	532	D	3.14
A-482		486.3	486.5	D	3.31
A-483		483.87	484.5	D	2.63

TABLE 2-continued

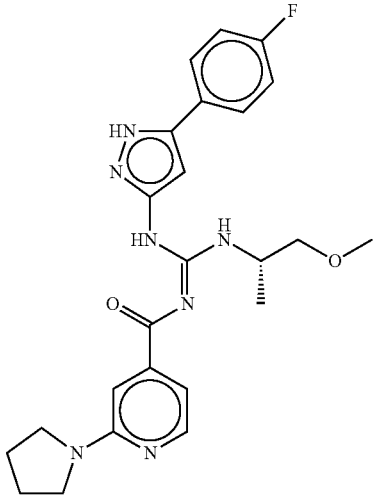
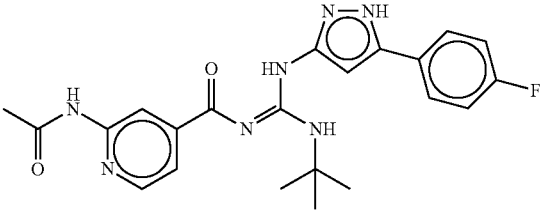
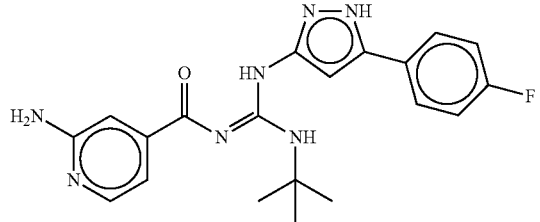
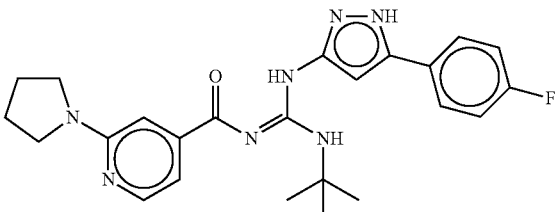
Compound No.	Chemical Structure	Calculated	MS	HPLC	HPLC
		MW (g/mol)	(m/z)	Method	Retention Time (min)
A-484		465.52	466.26	A	6.49
A-485		437.47	460.23 (M + Na + 1) <sup>+</sup>	A	7.45
A-486		395.43	396.11	A	6.95
A-487		449.52	448.29 (M - H) <sup>-</sup>	A	7.72

TABLE 2-continued

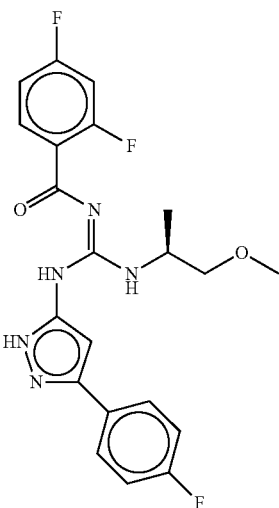
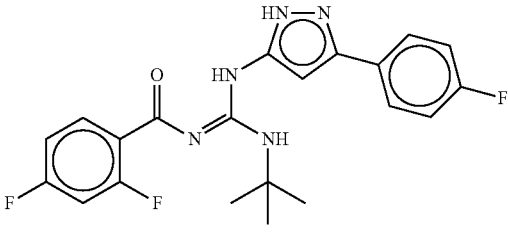
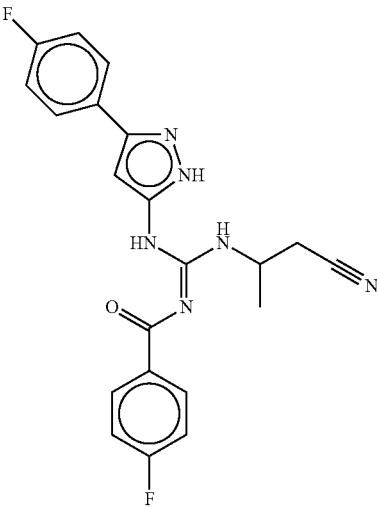
Compound No.	Chemical Structure	Calculated		HPLC	
		MW (g/mol)	MS (m/z)	HPLC Method	Retention Time (min)
A-488		431.41	430.03 (M - 1) <sup>-</sup>	E	8.68
A-489		415.41	414.07 (M - 1) <sup>-</sup>	E	9.62
A-490		408.4	407.08 (M - H) <sup>-</sup>	E	8.93

TABLE 2-continued

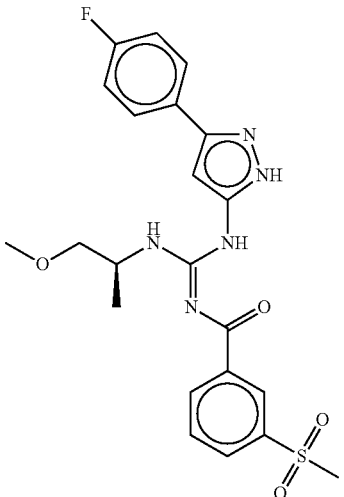
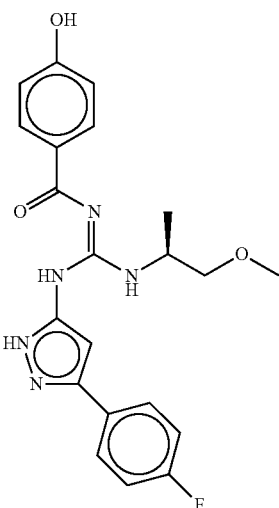
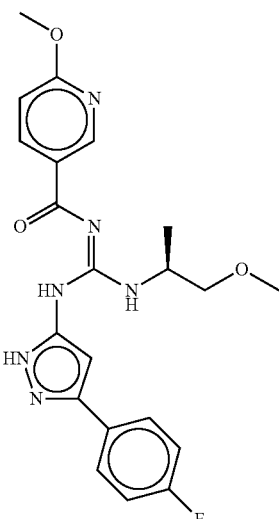
Compound No.	Chemical Structure	Calculated MW (g/mol)	MS (m/z)	HPLC Method	HPLC Retention Time (min)
A-491		473.52	472.06 (M - H) <sup>-</sup>	E	8.27
A-492		411.43	410.09 (M - H) <sup>-</sup>	E	8.24
A-493		426.44	425.08 (M - H) <sup>-</sup>	E	8.5

TABLE 2-continued

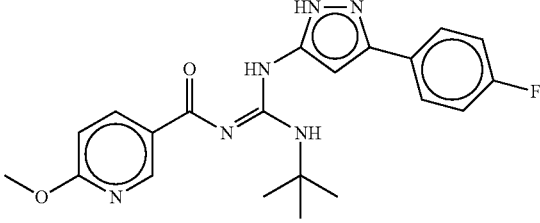
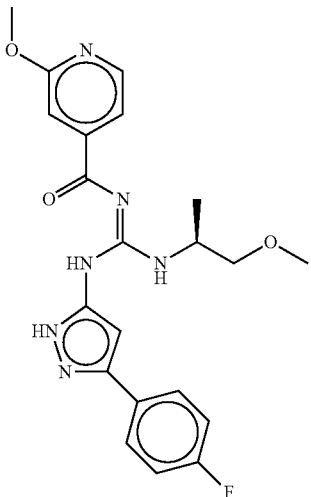
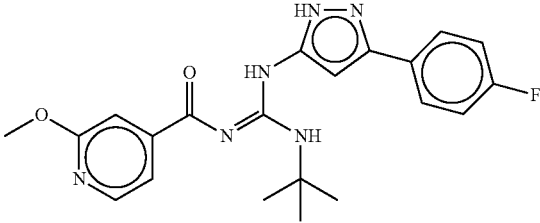
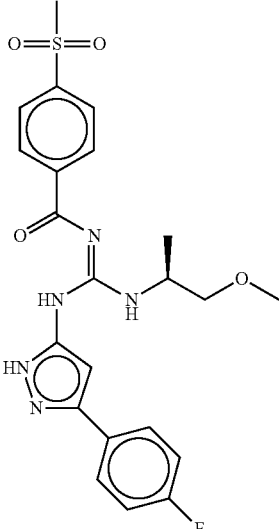
Compound No.	Chemical Structure	Calculated MW (g/mol)	MS (m/z)	HPLC Method	HPLC Retention Time (min)
A-494		410.44	409.10 (M - H) <sup>-</sup>	E	9.6
A-495		426.44	425.08 (M - H) <sup>-</sup>	E	8.68
A-496		410.44	409.10 (M - H) <sup>-</sup>	E	10.65
A-497		473.52	472.06 (M - H) <sup>-</sup>	A	8.36

TABLE 2-continued

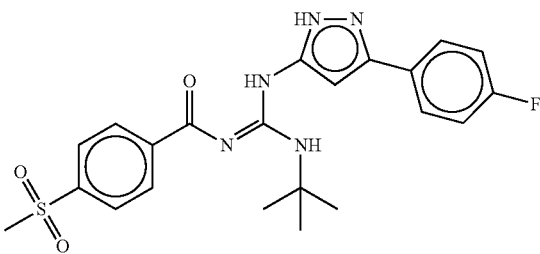
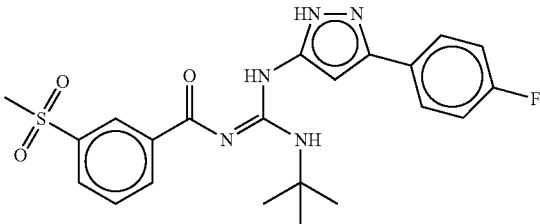
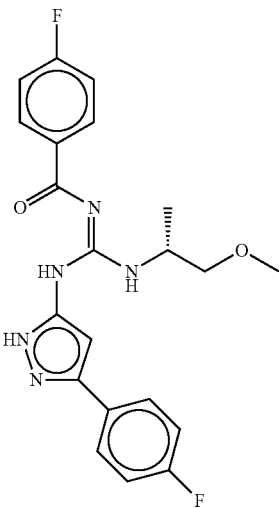
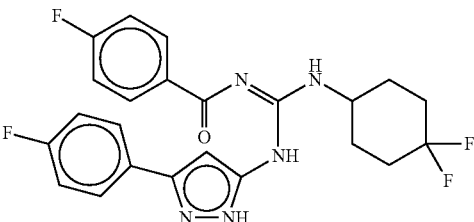
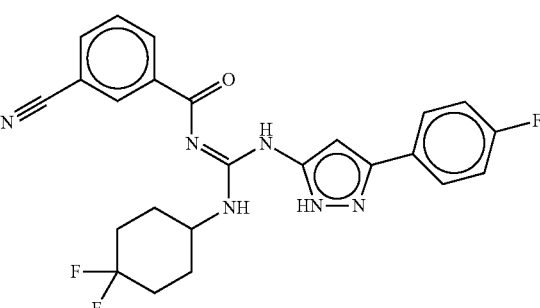
Compound No.	Chemical Structure	Calculated MW (g/mol)	MS (m/z)	HPLC Method	HPLC Retention Time (min)
A-498		457.52	456.06 (M - H) <sup>-</sup>	A	9.8
A-499		457.52	456.08 (M - H) <sup>-</sup>	A	9.85
A-500		413.42	412.10 (M - H) <sup>-</sup>	A	8.76
A-501		459.44	458.04 (M - H) <sup>-</sup>	A	9.27
A-502		466.46	465.04 (M - H) <sup>-</sup>	A	9.79



TABLE 2-continued

Compound No.	Chemical Structure	Calculated	MS (m/z)	HPLC Method	HPLC Retention
		MW (g/mol)			Time (min)
A-503		489.8	489.96, 491.95	A	12.2
A-504		434.47	433.09 (M - H) <sup>-</sup>	A	9.22
A-505		427.45	426.07 (M - H) <sup>-</sup>	A	9.08
A-506		478.52	477.11 (M - H) <sup>-</sup>	A	8.04
A-507		471.5	470.11 (M - H) <sup>-</sup>	A	7.8
A-508		404.44	403.11 (M - H) <sup>-</sup>	A	7.86

TABLE 2-continued

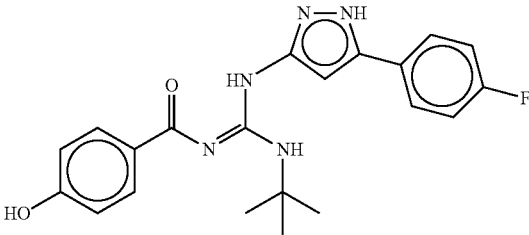
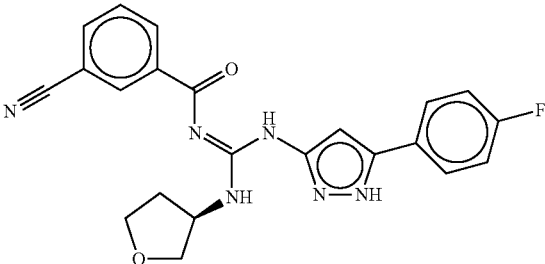
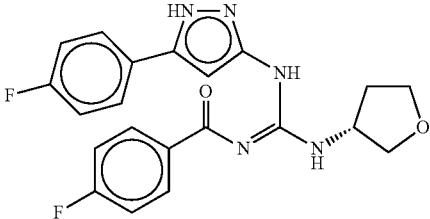
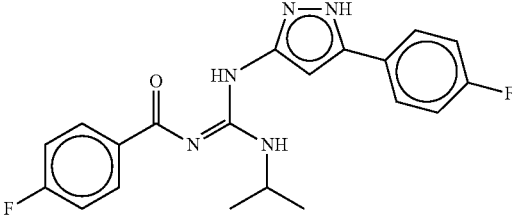
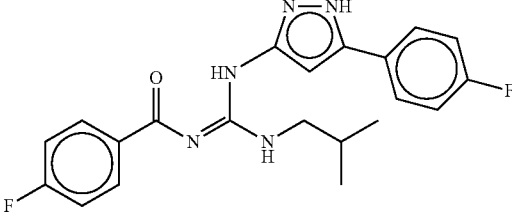
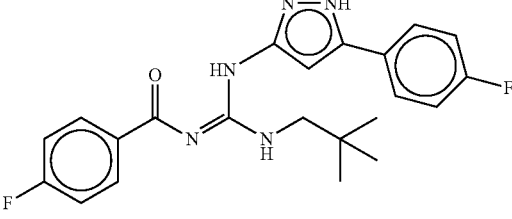
Compound No.	Chemical Structure	Calculated MW (g/mol)	MS (m/z)	HPLC Method	HPLC Retention Time (min)
A-509		395.43	394.09 (M - H) <sup>-</sup>	A	7.06
A-510		418.42	417.02 (M - H) <sup>-</sup>	A	7.55
A-511		411.4	410.03 (M - H) <sup>-</sup>	A	7.01
A-512		383.39	382.07 (M - H) <sup>-</sup>	A	7.48
A-513		397.42	396.1 (M - H) <sup>-</sup>	A	7.88
A-514		411.45	410.07 (M - H) <sup>-</sup>	A	8.24

TABLE 2-continued

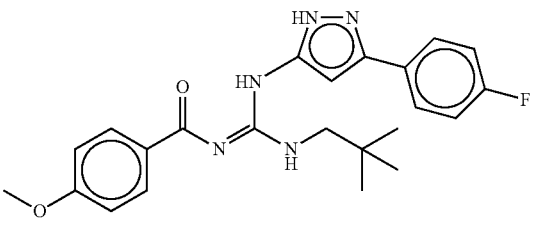
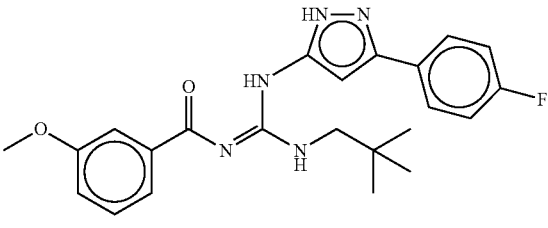
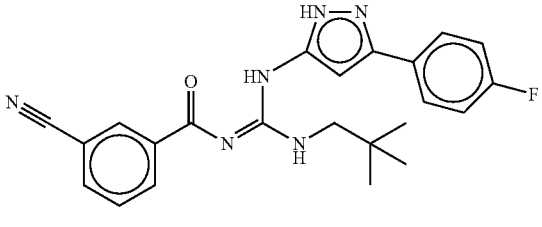
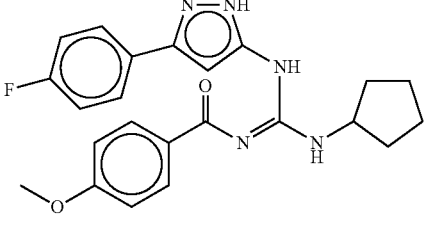
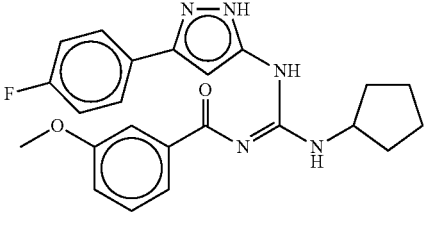
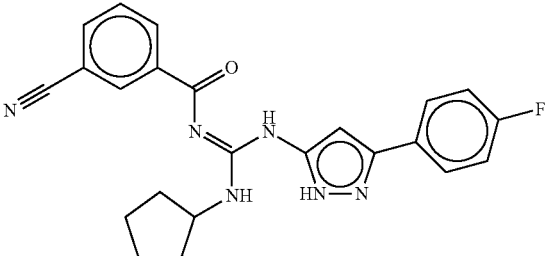
Compound No.	Chemical Structure	Calculated MW (g/mol)	MS (m/z)	HPLC Method	HPLC Retention Time (min)
A-515		423.48	422.03 (M - H) <sup>-</sup>	A	8.28
A-516		423.48	422.03 (M - H) <sup>-</sup>	A	8.23
A-517		418.47	417.02 (M - H) <sup>-</sup>	A	8.4
A-518		421.47	420.01 (M - H) <sup>-</sup>	A	8.07
A-519		421.47	420.01 (M - H) <sup>-</sup>	A	8
A-520		416.45	414.98 (M - H) <sup>-</sup>	A	8

TABLE 2-continued

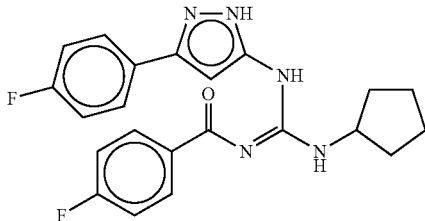
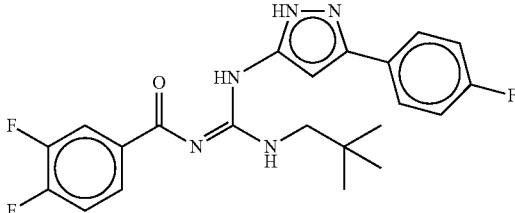
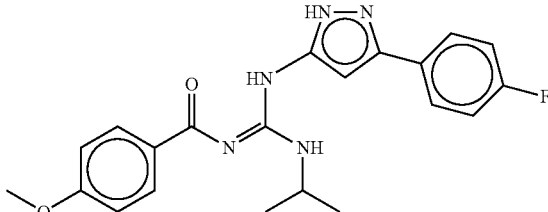
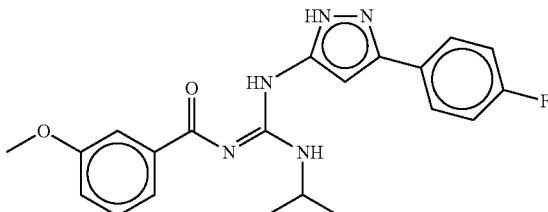
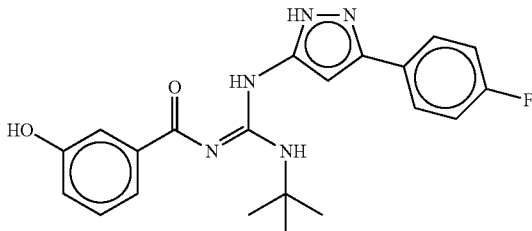
Compound No.	Chemical Structure	Calculated	MS	HPLC	HPLC
		MW (g/mol)	(m/z)	Method	Retention Time (min)
A-521		409.43	407.99 (M - H) <sup>-</sup>	A	7.98
A-522		429.44	428.00 (M - H) <sup>-</sup>	A	8.73
A-523		395.43	394.02 (M - H) <sup>-</sup>	A	7.51
A-524		395.43	394.02 (M - H) <sup>-</sup>	A	7.44
A-525		395.43	394.02 (M - H) <sup>-</sup>	A	7.06

TABLE 2-continued

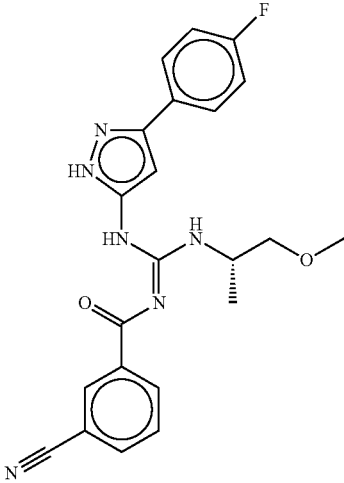
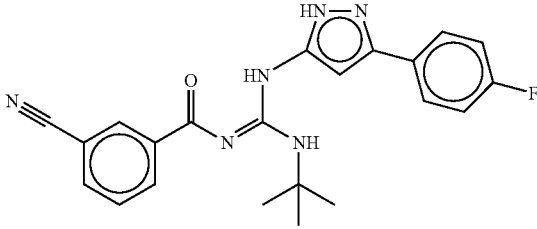
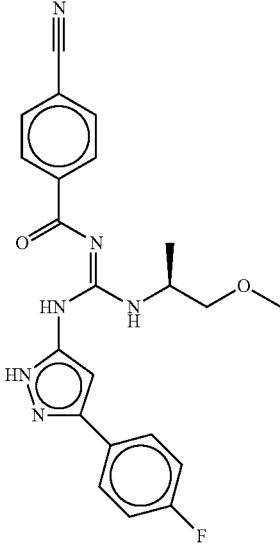
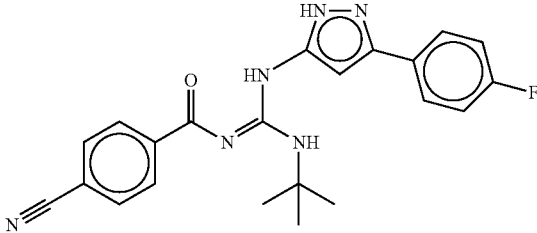
Compound No.	Chemical Structure	Calculated MW (g/mol)	MS (m/z)	HPLC Method	HPLC Retention Time (min)
A-526		420.44	419.10 (M - H) <sup>-</sup>	A	7.66
A-527		404.44	403.12 (M - H) <sup>-</sup>	A	10.39
A-528		420.44	419.10 (M - H) <sup>-</sup>	A	7.6
A-529		404.44	403.12 (M - H) <sup>-</sup>	A	10.27

TABLE 2-continued

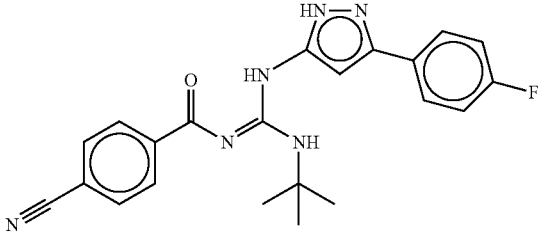
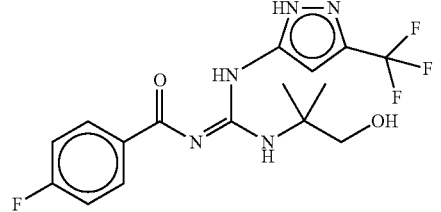
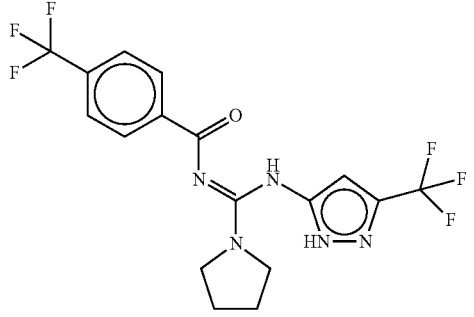
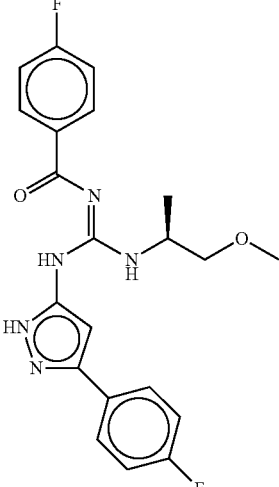
Compound No.	Chemical Structure	Calculated	MS (m/z)	HPLC Method	HPLC Retention
		MW (g/mol)			Time (min)
A-530		441.47	440.16 (M - H) <sup>-</sup>	A	6.98
A-531		387.33	NA	A	6.6
A-532		419.32	419.95	A	6.84
A-533		413.42	414.03	A	7.26

TABLE 2-continued

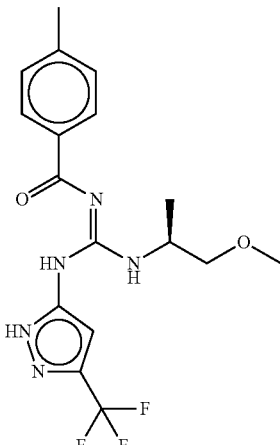
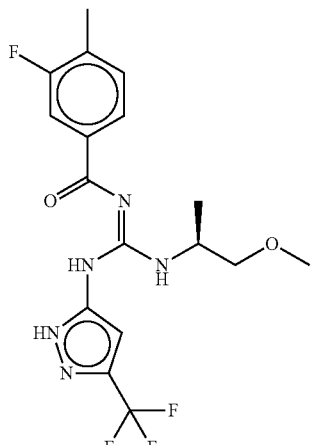
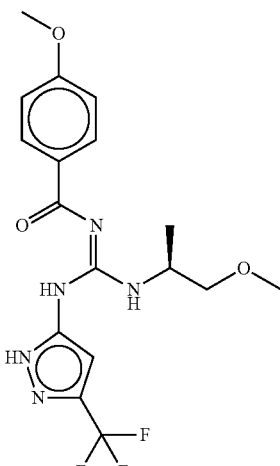
Compound No.	Chemical Structure	Calculated	MS (m/z)	HPLC Method	HPLC
		MW (g/mol)			Retention Time (min)
A-534		383.37	384.02	A	6.9
A-535		401.36	402.01	A	7.6
A-536		399.37	400	A	6.6

TABLE 2-continued

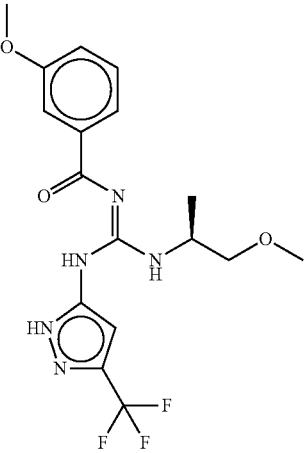
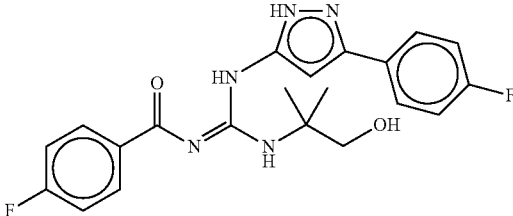
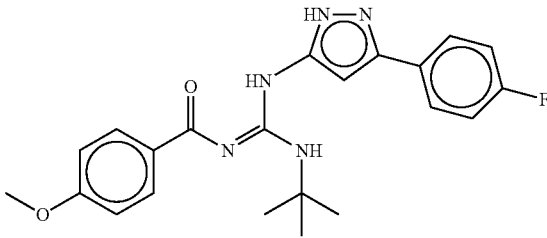
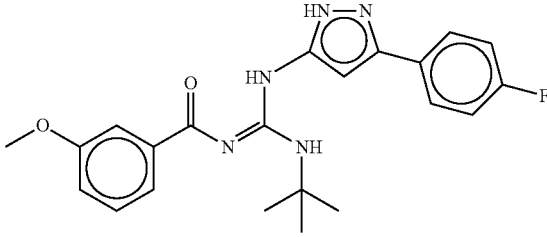
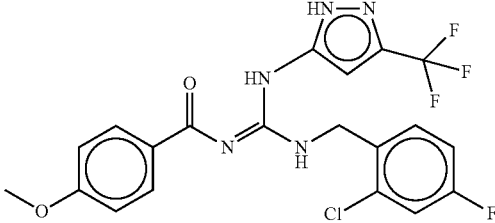
Compound No.	Chemical Structure	Calculated	MS (m/z)	HPLC Method	HPLC Retention
		MW (g/mol)			Time (min)
A-537		399.37	400	A	6.74
A-538		413.42	412.18 (M - H) <sup>-</sup>	A	7.28
A-539		409.46	410.07	A	7.83
A-540		409.46	410.07	A	8.24
A-541		469.82	469.92, 471.9	A	8.41



TABLE 2-continued

Compound No.	Chemical Structure	Calculated MW (g/mol)	MS (m/z)	HPLC Method	HPLC Retention Time (min)
A-542		469.82	469.92, 471.9	A	9.07
A-543		469.82	469.92, 471.9 (M - H) <sup>-</sup>	A	9.17
A-544		353.34	352.17 (M - H) <sup>-</sup>	A	8.8
A-545		365.35	364.18 (M - H) <sup>-</sup>	A	7.04
A-546		397.37	396.17 (M - H) <sup>-</sup>	A	8.08
A-547		379.38	378.16 (M - H) <sup>-</sup>	A	7.44

TABLE 2-continued

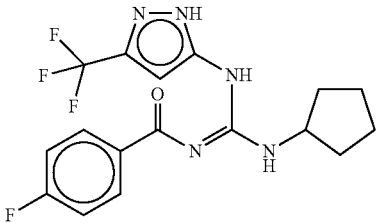
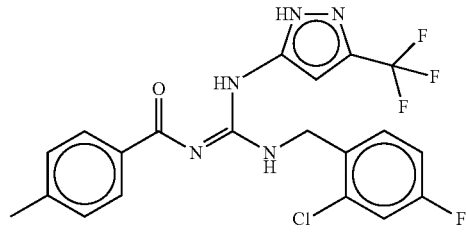
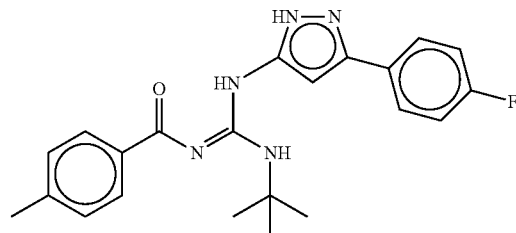
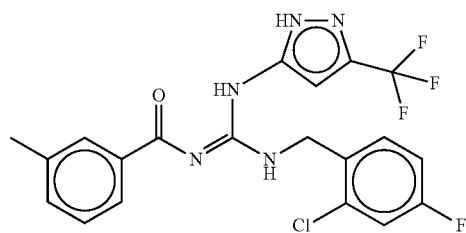
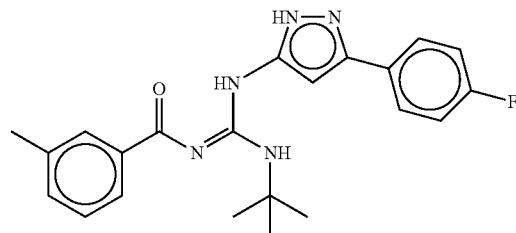
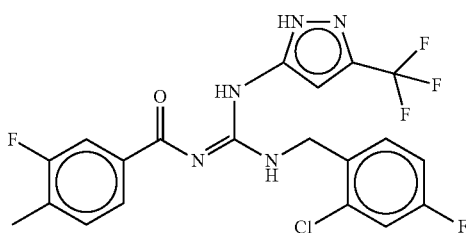
Compound No.	Chemical Structure	Calculated MW (g/mol)	MS (m/z)	HPLC Method	HPLC Retention Time (min)
A-548		383.34	382.19 (M - H) <sup>-</sup>	A	7.49
A-549		453.82	452.10, 454.11 (M - H) <sup>-</sup>	A	8.91
A-550		393.46	392.25 (M - H) <sup>-</sup>	A	8.27
A-551		453.82	452.15, 454.15 (M - H) <sup>-</sup>	A	9.56
A-552		393.46	392.26 (M - H) <sup>-</sup>	A	8.4
A-553		471.81	470.13, 472.12 (M - H) <sup>-</sup>	A	10.86

TABLE 2-continued

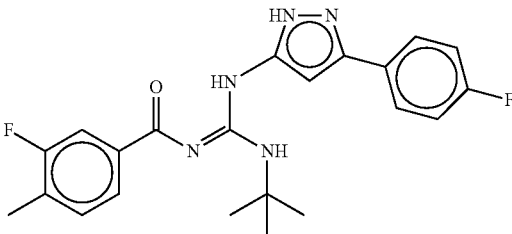
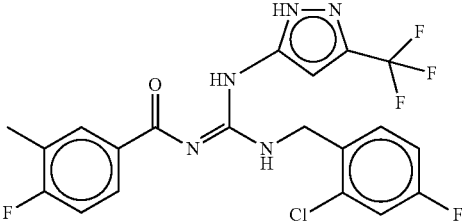
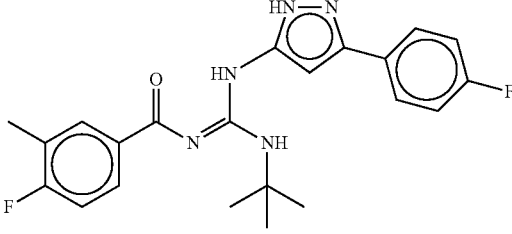
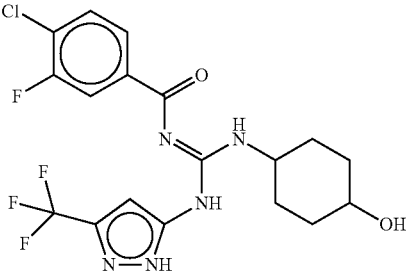
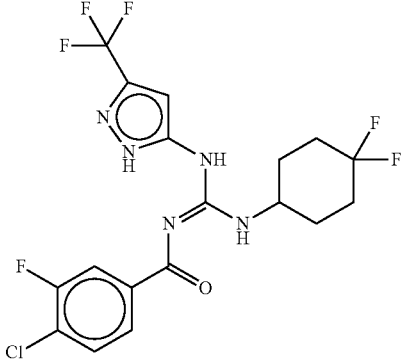
Compound No.	Chemical Structure	Calculated	MS	HPLC Method	HPLC Retention
		MW (g/mol)	(m/z)		Time (min)
A-554		411.45	410.27 (M - H) <sup>-</sup>	A	10.05
A-555		471.81	470.10, 472.09 (M - H) <sup>-</sup>	A	10.39
A-556		411.45	410.21 (M - H) <sup>-</sup>	A	9.34
A-557		447.81	448	D	1.9
A-558		467.8	468	D	2.5

TABLE 2-continued

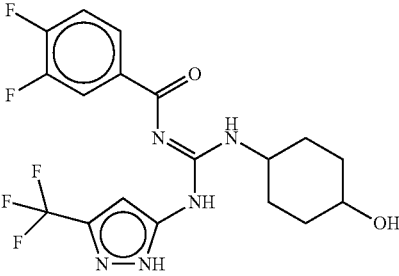
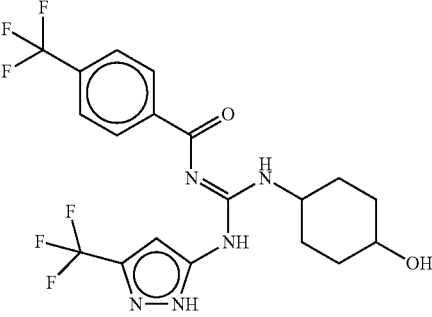
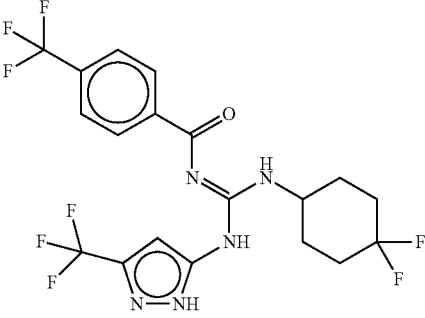
Compound No.	Chemical Structure	Calculated	MS (m/z)	HPLC Method	HPLC Retention
		MW (g/mol)			Time (min)
A-559		431.36	432	D	1.76
A-560		463.38	464	D	1.9
A-561		483.36	484	D	2.45
A-571		477.45	NA	NA	NA

TABLE 2-continued

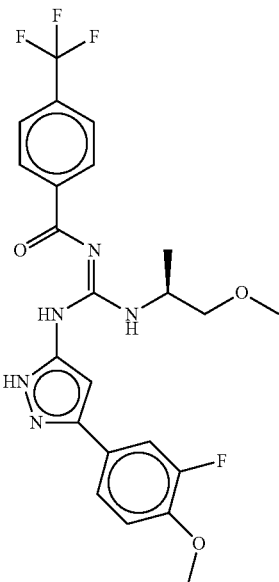
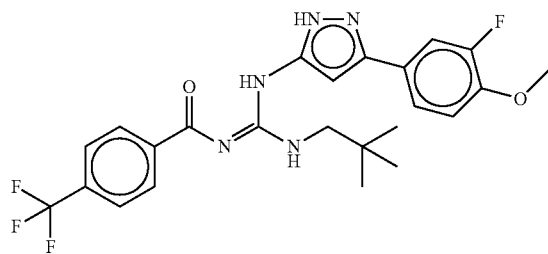
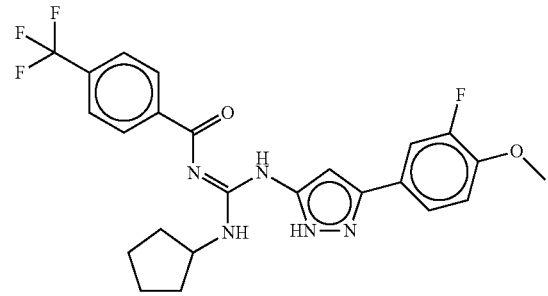
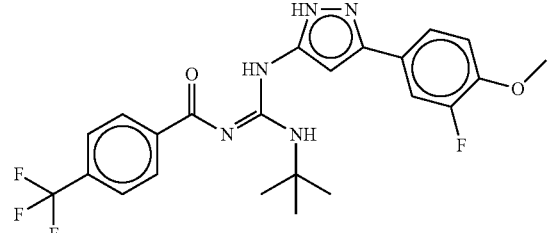
Compound No.	Chemical Structure	Calculated	MS (m/z)	HPLC Method	HPLC Retention
		MW (g/mol)			Time (min)
A-572		493.45	NA	NA	NA
A-573		491.48	NA	NA	NA
A-574		489.47	NA	NA	NA
A-575		477.45	NA	NA	NA

TABLE 2-continued

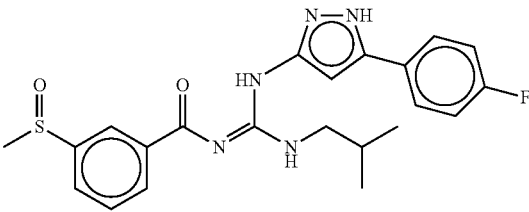
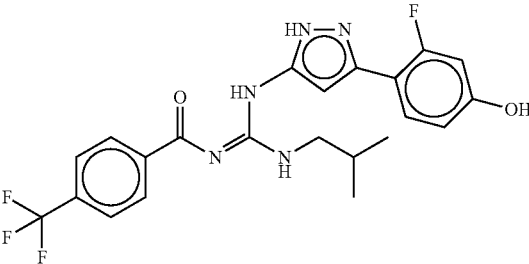
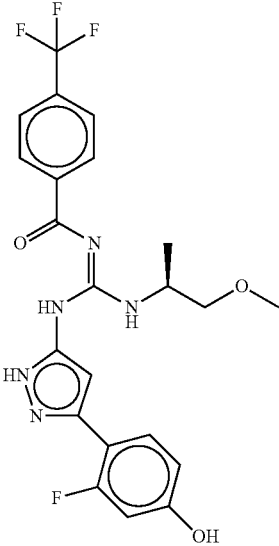
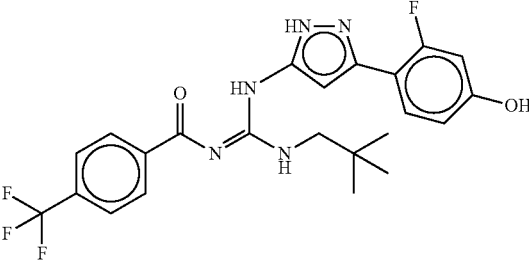
Compound No.	Chemical Structure	Calculated	MS	HPLC	HPLC
		MW (g/mol)	(m/z)	Method	Retention Time (min)
A-576		441.52	NA	NA	NA
A-577		463.43	NA	NA	NA
A-578		479.43	NA	NA	NA
A-579		477.45	NA	NA	NA

TABLE 2-continued

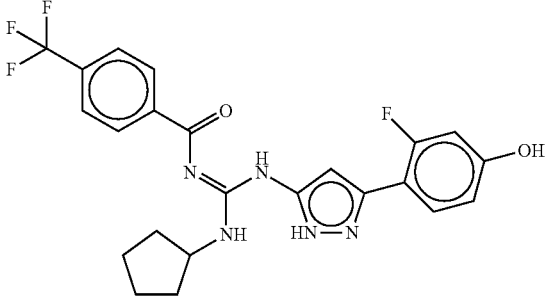
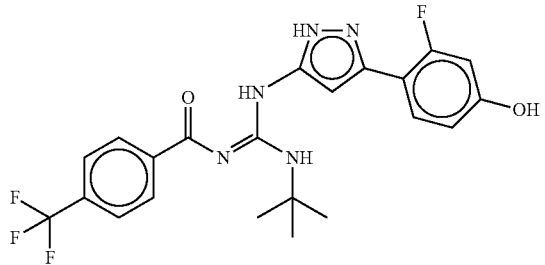
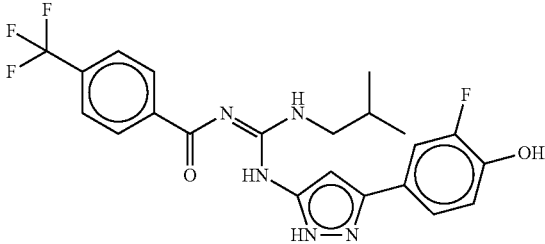
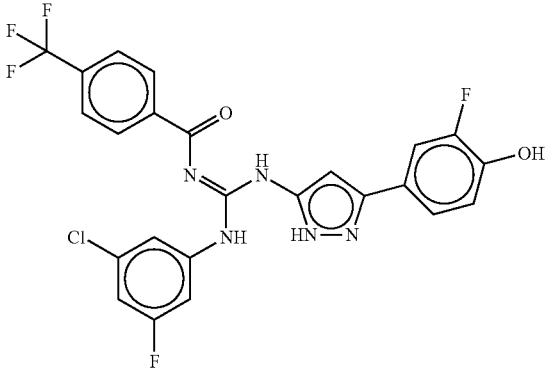
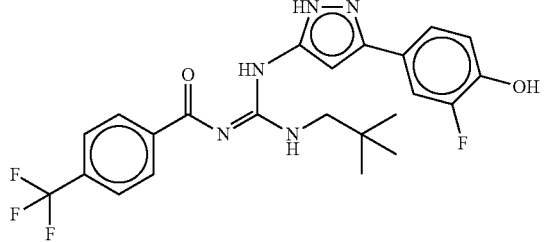
Compound No.	Chemical Structure	Calculated MW (g/mol)	MS (m/z)	HPLC Method	HPLC Retention Time (min)
A-580		475.44	NA	NA	NA
A-581		463.43	NA	NA	NA
A-582		463.43	NA	NA	NA
A-583		535.85	NA	NA	NA
A-584		477.45	NA	NA	NA

TABLE 2-continued

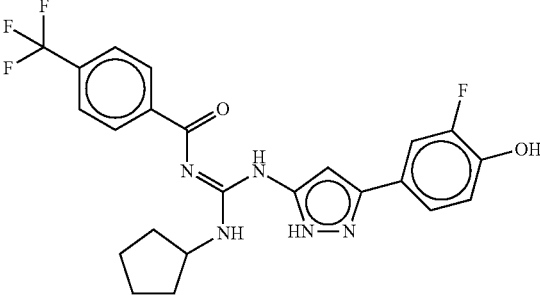
Compound No.	Chemical Structure	Calculated	MS (m/z)	HPLC Method	HPLC Retention
		MW (g/mol)			Time (min)
A-585		475.44	NA	NA	NA

TABLE 3

Compound No.	NMR Solvent	<sup>1</sup> H NMR Resonance Data (δ)
A-4	DMSO-d <sup>6</sup>	14.21 (bs, 0.5H), 12.82 (bs, 0.5H), 12.73 (s, 0.5H), 10.02 (s, 0.5H), 8.67 (bs, 0.5H), 8.07 (bs, 1.5H), 7.80 (d, 1H), 7.57-7.51 (m, 2H), 7.37 (s, 0.5H), 6.82 (bs, 1H), 5.83 (s, 0.5H), 1.52 (s, 6H), 1.38 (s, 3H).
A-37	DMSO-d <sup>6</sup>	13.62 (s, 1H), 12.20 (bs, 0.3H), 8.59 (m, 1H), 8.38 (bs, 1H), 8.12 (d, 1H), 7.92 (d, 1H), 7.64 (d, 1H), 7.52 (d, 1H), 1.54 (s, 5H), 1.46 (s, 4H).
A-40	DMSO-d <sup>6</sup>	13.60 (br s, 1H), 8.55 (br s, 1H), 7.88 (m, 2H), 7.68 (m, 1H), 6.77 (m, 1H), 5.85 (br s, 1H), 1.5 (s, 6H).
A-41	DMSO-d <sup>6</sup>	13.40-12.40 (br m, 1H), 10.62-10.12 (br m, 1H), 9.38-8.60 (br m, 1H), 8.00-7.40 (br m, 3H), 6.85-6.40 (br m, 1H), 4.40-3.80 (br m, 1H), 1.95 (bs, 2H), (bm, 11H).
A-44	DMSO-d <sup>6</sup>	12.68 (bs, 1H), 8.55 (bs, 1H), 7.93 (m, 2H), 7.51 (q, 1H, J = 8.4 Hz), 6.86 (s, 1H), 3.90 (s, 3H), 1.53 (s, 9H).
A-45	DMSO-d <sup>6</sup>	12.61 (s, 1H), 12.54 (s, 1H), 11.03 (s, 1H), 7.89 (m, 2H), 7.66 (s, 1H), 7.55 (m, 2H), 7.24 (d, 1H, J = 8.8 Hz), 2.24 (s, 3H).
A-48	DMSO-d <sup>6</sup>	10.86 (s, 1H), 10.22 (s, 1H), 8.04 (d, 2H, J = 8.0 Hz), 7.93 (d, 2H, J = 8.0 Hz), 7.65 (m, 2H), 7.11 (d, 1H, J = 8.4 Hz), 6.05 (s, 1H), 3.74 (s, 3H).
A-49	DMSO-d <sup>6</sup>	8.18 (d, 2H, J = 8 Hz), 7.90-7.79 (m, 4H), 7.49 (dd, 2H, J = 8.8, 5.2), 7.17 (t, 2H, J = 8.8 Hz), 5.56 (bs, 2H), 1.45 (s, 9H).
A-50	DMSO-d <sup>6</sup>	13.25 (s, 1H), 12.84 (s, 1H), 9.01 (s, 1H), 8.28 (d, 2H, J = 8.0 Hz), 7.83 (d, 2H, J = 8.0 Hz), 7.79 (dd, 2H, J = 8.8, 5.2 Hz), 7.32 (t, 2H, J = 8.8 Hz), 6.60 (s, 1H), 1.56 (s, 9H).
A-53	DMSO-d <sup>6</sup>	13.59 (br s, 1H), 12.72 (s, 1H), 8.87 (s, 1H), 8.27 (d, 2H), 7.84 (d, 2H), 7.16 (t, 1H), 6.50 (s, 1H), 1.54 (s, 9H).
A-54	DMSO-d <sup>6</sup>	13.57 (br s, 1H), 12.78 (br s, 1H), 8.79 (br s, 1H), 8.08 (m, 2H), 7.57 (m, 2H), 7.15 (t, 1H), 6.48 (s, 1H), 1.52 (s, 9H).
A-55	DMSO-d <sup>6</sup>	13.52 (br s, 1H), 12.58 (br s, 1H), 8.54 (br s, 1H), 8.1 (m, 2H), 7.48 (m, 2H), 7.16 (t, 1H), 6.50 (s, 1H), 4.4 (m, 1H), 1.24 (m, 6H).
A-56	DMSO-d <sup>6</sup>	13.52 (br s, 1H), 12.55 (br s, 1H), 8.94 (br s, 1H), 8.07 (m, 2H), 7.62 (m, 1H), 7.5-7.35 (m, 4H), 6.54 (s, 1H), 4.75 (br m, 2H).
A-58	DMSO-d <sup>6</sup>	13.55 (br s, 1H), 12.52 (br s, 1H), 8.6 (br s, 1H), 8.29 (m, 2H), 7.79 (m, 2H), 7.16 (t, 1H), 6.52 (s, 1H), 4.41 (m, 1H), 1.26 (m, 6H).
A-62	DMSO-d <sup>6</sup>	13.58 (br s, 1H), 12.65 (br s, 1H), 8.84 (s, 1H), 7.95 (m, 2H), 7.53 (m, 1H), 7.15 (t, 1H), 6.48 (s, 1H), 1.52 (s, 9H).
A-63	DMSO-d <sup>6</sup>	13.55 (br s, 1H), 12.46 (br s, 1H), 8.6 (br s, 1H), 8.01 (m, 2H), 7.48 (m, 1H), 7.16 (t, 1H), 6.50 (s, 1H), 4.39 (m, 1H), 1.25 (m, 6H).
A-65	DMSO-d <sup>6</sup>	13.6 (br s, 1H), 12.63 (br s, 1H), 8.86 (br s, 1H), 7.91 (m, 2H), 7.71 (m, 1H), 7.16 (t, 1H), 6.49 (s, 1H), 1.52 (s, 9H).
A-69	DMSO-d <sup>6</sup>	13.6 (br s, 1H), 12.64 (br s, 1H), 8.87 (br s, 1H), 8.10 (m, 2H), 7.48 (m, 2H), 7.16 (t, 1H), 6.51 (s, 1H), 3.44 (m, 2H), 0.96 (s, 9H).
A-125	DMSO-d <sup>6</sup>	12.59 (s, 1H), 12.45 (d, J = 1 Hz, 1H), 9.04 (s, 1H), 8.24 (d, J = 8 Hz, 2H), 7.80 (d, J = 8 Hz, 2H), 5.84 (d, J = 8 Hz, 1H), 1.51 (s, 9H).
A-127	DMSO-d <sup>6</sup>	13.24 (s, 1H), 12.59 (s, 1H), 8.82 (d, J = 6.7 Hz, 1H), 8.41 (m, 2H), 7.96 (d, J = 7.6 Hz, 1H), 7.76 (m, 2H), 7.67 (t, J = 7.6 Hz, 1H), 7.32 (t, J = 8.6 Hz, 2H), 6.61 (s, 1H), 4.44 (q, J = 6.7 Hz, 1H), 1.29 (d, J = 6.3 Hz, 6H).
A-155	DMSO-d <sup>6</sup>	12.54 (s, 1H), 12.50 (s, 1H), 9.18 (t, 1H), 8.30 (d, 2H), 7.80 (d, 2H), 5.93 (s, 1H), 3.47 (d, 2H), 2.23 (s, 3H), 0.98 (s, 3H).



TABLE 3-continued

Compound No.	NMR Solvent	<sup>1</sup> H NMR Resonance Data (δ)
A-158	DMSO-d <sup>6</sup>	13.18 (s, 1H), 12.58 (s, 1H), 8.95 (d, 1H), 8.00 (m, 2H), 7.70 (d, 2H), 7.49 (m, 1H), 7.40 (d, 2H), 6.57 (s, 1H), 5.22 (m, 1H), 4.53 (m, 3H), 2.05 (m, 2H), 1.60 (m, 6H).
A-159	DMSO-d <sup>6</sup>	13.20 (s, 1H), 12.78 (s, 1H), 9.00 (s, 1H), 7.96 (m, 2H), 7.70 (d, 2H), 7.53 (m, 1H), 7.40 (d, 2H), 6.58 (s, 1H), 5.23 (t, 1H), 4.50 (d, 2H), 1.55 (s, 9H).
A-160	DMSO-d <sup>6</sup>	13.32 (s, 1H), 12.65 (s, 1H), 8.22 (t, 1H), 8.00 (m, 2H), 7.70 (d, 2H), 7.60 (d, 2H), 7.50 (m, 1H), 3.62 (m, 2H), 3.42 (m, 5H), 1.81 (m, 2H), 1.10 (m, 3H).
A-162	DMSO-d <sup>6</sup>	13.41 (s, 1H), 13.15 (s, 1H), 8.44 (s, 1H), 7.97 (m, 2H), 7.70 (d, 2H), 7.60 (d, 2H), 7.55 (m, 1H), 1.54 (s, 9H).
A-163	DMSO-d <sup>6</sup>	13.11 (s, 1H), 12.80 (s, 1H), 8.86 (s, 1H), 8.75 (t, 1H), 8.14 (m, 1H), 7.79 (t, 2H), 7.30 (t, 2H), 6.80 (d, 1H), 6.56 (s, 1H), 3.65 (m, 4H), 3.52 (m, 4H), 3.40 (m, 2H), 1.92 (m, 1H), 0.95 (d, 6H).
A-164	DMSO-d <sup>6</sup>	13.20 (s, 1H), 12.97 (s, 1H), 8.82 (s, 1H), 8.79 (s, 1H), 8.10 (d, 1H), 7.79 (t, 2H), 7.31 (t, 2H), 6.82 (d, 1H), 6.52 (s, 1H), 3.98 (m, 1H), 3.65 (m, 4H), 3.55 (m, 4H), 1.55 (s, 9H).
A-171	DMSO-d <sup>6</sup>	13.18 (s, 1H), 12.80 (s, 1H), 8.84 (t, 1H), 7.80-7.65 (m, 4H), 7.32 (m, 3H), 7.03 (m, 1H), 6.59 (s, 1H), 3.78 (s, 3H), 3.42 (m, 2 H), 1.95 (m, 1H), 0.96 (d, 6H).
A-173	DMSO-d <sup>6</sup>	13.08 (s, 1H), 10.46 (s, 1H), 9.72 (s, 1H), 7.95 (t, 2H), 7.65 (d, 2H), 7.40 (t, 2H), 7.20 (d, 2H), 5.95 (s, 1H), 3.60 (m, 5H).
A-174	DMSO-d <sup>6</sup>	13.23 (s, 1H), 12.60 (s, 1H), 8.82 (d, 1H), 8.58 (d, 1H), 7.78 (m, 4H), 7.33 (t, 2H), 6.60 (s, 1H), 4.30 (m, 1H), 2.80 (m, 2H), 1.62 (m, 2H), 1.24 (m, 6H), 0.95 (m, 3H).
A-176	DMSO-d <sup>6</sup>	13.20 (s, 1H), 12.59 (s, 1H), 8.98 (t, 1H), 8.58 (d, 1H), 7.80 (m, 4H), 7.33 (t, 2H), 6.61 (s, 1H), 3.45 (m, 2H), 2.80 (m, 2H), 1.93 (m, 1H), 1.22 (t, 3H), 0.98 (d, 6H).
A-177	DMSO-d <sup>6</sup>	13.25 (s, 1H), 12.75 (s, 1H), 9.02 (s, 1H), 8.60 (s, 1H), 7.79 (m, 4H), 7.31 (t, 2H), 6.60 (s, 1H), 3.15 (s, 2H), 2.81 (q, 2H), 1.57 (s, 9H), 1.23 (t, 3H).
A-206	DMSO-d <sup>6</sup>	13.22 (s, 1H), 12.78 (s, 1H), 8.75 (d, 1H), 8.19 (t, 2H), 7.79 (t, 2H), 7.34 (t, 2H), 7.22 (t, 2H), 6.60 (s, 1H), 4.27 (m, 1H), 1.60 (m, 2H), 1.23 (d, 3H), 0.95 (t, 3H).
A-209	DMSO-d <sup>6</sup>	13.28 (s, 1H), 12.78 (s, 1H), 8.72 (d, 1H), 8.19 (t, 2H), 7.78 (d, 2H), 7.55 (d, 2H), 7.23 (t, 2H), 6.63 (s, 1H), 4.28 (m, 1H), 1.60 (m, 2H), 1.23 (d, 3H), 0.94 (t, 3H).
A-213	DMSO-d <sup>6</sup>	13.15 (s, 1H), 12.61 (s, 1H), 9.06 (t, 1H), 7.98 (t, 2H), 7.80 (t, 2H), 7.64 (t, 1H), 7.33 (t, 2H), 6.60 (s, 1H), 3.81 (m, 1H), 3.66 (m, 1H), 3.50 (m, 3H), 1.13 (m, 6H).
A-214	DMSO-d <sup>6</sup>	13.20 (s, 1H), 12.63 (s, 1H), 9.00 (t, 1H), 8.00 (m, 2H), 7.78 (d, 2H), 7.50 (m, 3H), 6.62 (s, 1H), 3.82 (m, 1H), 3.65 (m, 1H), 3.50 (m, 3H), 1.15 (m, 6H).
A-216	DMSO-d <sup>6</sup>	13.22 (s, 1H), 12.58 (s, 1H), 8.80 (d, 1H), 7.95 (d, 2H), 7.79 (t, 2H), 7.64 (m, 1H), 7.33 (t, 2H), 6.60 (s, 1H), 4.40 (septet, 1H), 1.27 (d, 6H).
A-218	DMSO-d <sup>6</sup>	13.22 (s, 1H), 12.61 (s, 1H), 9.00 (d, 1H), 7.97 (m, 2H), 7.78 (t, 2H), 7.65 (m, 1H), 7.30 (t, 2H), 6.60 (s, 1H), 4.55 (m, 1H), 3.46 (m, 2H), 3.30 (s, 3H), 3.12 (s, 1H), 1.22 (d, 3H).
A-219	DMSO-d <sup>6</sup>	13.22 (s, 1H), 12.60 (s, 1H), 8.80 (d, 1H), 7.94 (m, 2H), 7.80 (t, 2H), 7.63 (t, 1H), 7.32 (t, 2H), 6.60 (s, 1H), 4.27 (m, 1H), 1.60 (m, 2H), 1.22 (d, 3H), 0.93 (t, 3H).
A-220	DMSO-d <sup>6</sup>	13.20 (s, 1H), 12.59 (s, 1H), 8.95 (t, 1H), 7.95 (d, 2H), 7.80 (t, 2H), 7.65 (t, 1H), 7.32 (t, 2H), 6.60 (s, 1H), 3.23 (m, 2H), 1.92 (m, 1H), 0.97 (d, 6H).
A-221	DMSO-d <sup>6</sup>	13.21 (s, 1H), 12.57 (s, 1H), 8.96 (d, 1H), 7.97 (m, 2H), 7.80 (t, 2H), 7.64 (t, 1H), 7.32 (t, 2H), 6.60 (s, 1H), 4.54 (m, 1H), 2.05 (m, 2H), 1.60 (m, 6H).
A-222	DMSO-d <sup>6</sup>	13.22 (s, 1H), 12.52 (s, 1H), 9.02 (d, 1H), 7.96 (m, 2H), 7.80 (t, 2H), 7.65 (m, 1H), 7.33 (t, 2H), 6.60 (s, 1H), 4.62 (m, 1H), 2.40 (m, 2H), 2.00 (m, 2H), 1.75 (m, 2H).
A-225	DMSO-d <sup>6</sup>	13.30 (s, 1H), 12.62 (s, 1H), 8.77 (d, 1H), 7.99 (m, 2H), 7.73 (d, 2H), 7.50 (m, 3H), 6.62 (s, 1H), 4.28 (m, 1H), 1.60 (m, 2H), 1.23 (d, 3H), 0.94 (t, 3H).
A-230	DMSO-d <sup>6</sup>	13.40 (s, 1H), 12.75 (s, 1H), 8.62 (d, 1H), 8.11 (d, 2H), 7.49 (m, 4H), 7.27 (t, 1H), 6.75 (s, 1H), 4.40 (m, 1H), 1.27 (d, 6H).
A-231	DMSO-d <sup>6</sup>	13.40 (s, 1H), 12.70 (s, 1H), 8.86 (d, 1H), 8.13 (d, 2H), 7.50 (m, 4H), 7.28 (t, 1H), 6.78 (s, 1H), 4.62 (m, 1H), 2.40 (m, 2H), 2.00 (m, 2H), 1.75 (m, 2H).
A-233	DMSO-d <sup>6</sup>	13.38 (s, 1H), 12.78 (s, 1H), 8.80 (t, 1H), 8.10 (d, 2H), 7.50 (m, 4H), 7.29 (t, 1H), 6.77 (s, 1H), 3.43 (m, 2H), 1.93 (m, 1H), 0.96 (d, 6H).
A-234	DMSO-d <sup>6</sup>	13.40 (s, 1H), 12.79 (s, 1H), 8.65 (d, 1H), 8.10 (d, 2H), 7.50 (m, 4H), 7.29 (t, 1H), 6.78 (s, 1H), 4.27 (m, 1H), 1.60 (m, 2H), 1.22 (d, 3H), 0.93 (t, 3H).
A-235	DMSO-d <sup>6</sup>	13.15 (s, 1H), 12.61 (s, 1H), 9.00 (t, 1H), 8.00 (m, 2H), 7.80 (m, 2H), 7.47 (m, 1H), 7.32 (t, 2H), 6.60 (s, 1H), 3.78 (m, 2H), 3.60 (m, 2H), 3.48 (m, 2H), 1.12 (t, 3H).

TABLE 3-continued

Compound No.	NMR Solvent	<sup>1</sup> H NMR Resonance Data (δ)
A-240	DMSO-d <sup>6</sup>	13.26 (s, 1H), 12.64 (s, 1H), 8.93 (t, 1H), 8.30 (d, 2H), 7.80 (m, 4H), 7.57 (d, 2H), 6.65 (s, 1H), 3.46 (t, 2H), 1.93 (m, 1H), 0.98 (d, 6H).
A-241	DMSO-d <sup>6</sup>	13.30 (s, 1H), 12.63 (s, 1H), 8.78 (d, 1H), 8.29 (d, 2H), 7.78 (m, 4H), 7.55 (d, 2H), 6.63 (s, 1H), 4.42 (m, 1H), 1.30 (d, 6H).
A-242	DMSO-d <sup>6</sup>	13.33 (s, 1H), 12.81 (s, 1H), 8.82 (d, 1H), 8.18 (m, 2H), 7.52 (m, 2H), 7.25 (m, 3H), 6.75 (s, 1H), 4.52 (m, 1H), 3.51 (m, 4H), 1.28 (d, 3H), 1.13 (t, 3H).
A-243	DMSO-d <sup>6</sup>	13.38 (s, 1H), 12.78 (s, 1H), 8.80 (d, 1H), 8.20 (t, 2H), 7.50 (t, 2H), 7.22 (m, 3H), 6.75 (s, 1H), 4.52 (m, 1H), 2.03 (m, 2H), 1.60 (m, 6H).
A-244	DMSO-d <sup>6</sup>	13.33 (s, 1H), 12.80 (s, 1H), 8.78 (t, 1H), 8.18 (t, 2H), 7.52 (t, 2H), 7.22 (m, 3H), 6.77 (s, 1H), 3.43 (m, 2H), 1.91 (m, 1H), 0.97 (d, 6H).
A-245	DMSO-d <sup>6</sup>	13.38 (s, 1H), 12.80 (s, 1H), 8.60 (d, 1H), 8.18 (t, 2H), 7.50 (t, 2H), 7.25 (m, 3H), 6.74 (s, 1H), 4.40 (m, 1H), 1.27 (d, 6H).
A-246	DMSO-d <sup>6</sup>	13.40 (s, 1H), 12.69 (s, 1H), 8.88 (d, 1H), 8.00 (m, 2H), 7.72 (s, 1H), 7.62 (d, 1H), 7.47 (m, 2H), 6.78 (s, 1H), 4.55 (m, 1H), 3.48 (d, 2H), 3.30 (s, 3H), 1.25 (d, 3H).
A-249	DMSO-d <sup>6</sup>	13.19 (s, 1H), 12.71 (s, 1H), 8.89 (t, 1H), 8.11 (d, 2H), 7.80 (t, 2H), 7.48 (d, 2H), 7.32 (t, 2H), 6.60 (s, 1H), 3.42 (t, 2H), 1.92 (m, 1H), 0.98 (d, 6H).
A-250	DMSO-d <sup>6</sup>	13.21 (s, 1H), 12.70 (s, 1H), 8.72 (d, 1H), 8.12 (d, 2H), 7.78 (t, 2H), 7.47 (d, 2H), 7.31 (t, 2H), 6.60 (s, 1H), 4.40 (m, 1H), 1.27 (d, 6H).
A-254	DMSO-d <sup>6</sup>	13.24 (s, 1H), 12.75 (s, 1H), 8.83 (t, 1H), 8.19 (t, 2), 7.77 (d, 2H), 7.54 (d, 2H), 7.23 (t, 2H), 6.63 (s, 1H), 3.44 (t, 2H), 1.93 (m, 1H), 0.98 (d, 6H).
A-255	DMSO-d <sup>6</sup>	13.25 (s, 1H), 12.75 (s, 1H), 8.67 (d, 1H), 8.18 (t, 2H), 7.74 (d, 2H), 7.53 (d, 2H), 7.23 (t, 2H), 6.62 (s, 1H), 4.41 (m, 1H), 1.27 (d, 6H).
A-256	DMSO-d <sup>6</sup>	13.19 (s, 1H), 12.70 (s, 1H), 8.96 (d, 1H), 7.95 (d, 1H), 7.80 (m, 3H), 7.47 (t, 1H), 7.32 (m, 3H), 6.60 (s, 1H), 4.51 (m, 1H), 3.50 (m, 4H), 1.27 (d, 3H), 1.14 (t, 3H).
A-257	DMSO-d <sup>6</sup>	13.20 (s, 1H), 12.67 (s, 1H), 8.90 (t, 1H), 7.98 (d, 1H), 7.80 (m, 3H), 7.48 (m, 1H), 7.33 (m, 3H), 6.60 (s, 1H), 3.44 (m, 2H), 1.93 (m, 1H), 0.98 (d, 6H).
A-258	DMSO-d <sup>6</sup>	13.23 (s, 1H), 12.62 (s, 1H), 8.97 (d, 1H), 8.00 (m, 2H), 7.75 (d, 2H), 7.50 (m, 3H), 6.62 (s, 1H), 4.51 (m, 1H), 3.51 (m, 4H), 1.26 (d, 3H), 1.13 (t, 3H).
A-259	DMSO-d <sup>6</sup>	13.22 (s, 1H), 12.53 (s, 1H), 9.00 (d, 1H), 8.00 (m, 2H), 7.78 (m, 2H), 7.48 (m, 1H), 7.30 (m, 2H), 6.60 (s, 1H), 4.64 (m, 1H), 2.40 (m, 2H), 2.00 (m, 2H), 1.78 (m, 2H).
A-260	DMSO-d <sup>6</sup>	13.20 (s, 1H), 12.59 (s, 1H), 8.95 (d, 1H), 8.00 (m, 2H), 7.77 (m, 2H), 7.48 (m, 1H), 7.30 (t, 2H), 6.59 (s, 1H), 4.55 (m, 1H), 2.05 (m, 2H), 1.60 (m, 6H).
A-261	DMSO-d <sup>6</sup>	13.20 (s, 1H), 12.60 (s, 1H), 8.92 (t, 1H), 7.98 (m, 2H), 7.78 (m, 2H), 7.47 (m, 1H), 7.30 (t, 2H), 6.60 (s, 1H), 3.43 (t, 2H), 1.92 (m, 1H), 0.95 (d, 6H).
A-263	DMSO-d <sup>6</sup>	13.19 (s, 1H), 12.62 (s, 1H), 8.99 (d, 1H), 8.00 (m, 2H), 7.78 (m, 2H), 7.48 (m, 1H), 7.33 (t, 2H), 6.60 (s, 1H), 4.51 (m, 1H), 3.50 (m, 4H), 1.26 (d, 3H), 1.12 (t, 3H).
A-264	DMSO-d <sup>6</sup>	13.21 (s, 1H), 12.64 (s, 1H), 8.98 (d, 1H), 8.12 (d, 2H), 7.78 (t, 2H), 7.48 (d, 2H), 7.30 (t, 2H), 6.60 (s, 1H), 4.63 (m, 1H), 2.40 (m, 2H), 2.00 (m, 2H), 1.75 (m, 2H).
A-267	DMSO-d <sup>6</sup>	13.18 (s, 1H), 12.62 (s, 1H), 8.98 (d, 1H), 8.00 (m, 2H), 7.79 (t, 2H), 7.48 (m, 1H), 7.33 (t, 2H), 6.59 (s, 1H), 4.52 (m, 1H), 3.50 (m, 4H), 1.26 (d, 3H), 1.14 (t, 3H).
A-268	DMSO-d <sup>6</sup>	13.22 (s, 1H), 12.65 (s, 1H), 8.97 (d, 1H), 8.00 (m, 2H), 7.78 (t, 2H), 7.49 (m, 1H), 7.31 (t, 2H), 6.60 (s, 1H), 4.42 (m, 1H), 3.48 (m, 2H), 3.30 (s, 3H), 1.63 (m, 2H), 0.94 (t, 3H).
A-274	DMSO-d <sup>6</sup>	13.22 (s, 1H), 12.63 (s, 1H), 8.98 (d, 1H), 7.99 (m, 2H), 7.78 (t, 2H), 7.47 (m, 1H), 7.32 (t, 2H), 6.60 (s, 1H), 4.55 (m, 1H), 3.47 (d, 2H), 3.30 (s, 3H), 1.25 (d, 3H).
A-282	DMSO-d <sup>6</sup>	13.31 (s, 1H), 12.67 (s, 1H), 8.72 (t, 1H), 8.30 (d, 2H), 7.78 (d, 2H), 7.52 (t, 2H), 7.28 (m, 1H), 6.80 (s, 1H), 3.65 (m, 2H), 3.42 (m, 4H), 1.82 (m, 2H), 1.07 (t, 3H).
A-283	DMSO-d <sup>6</sup>	13.26 (s, 1H), 12.60 (s, 1H), 8.84 (t, 1H), 8.00 (m, 2H), 7.73 (s, 1H), 7.62 (d, 1H), 7.44 (m, 2H), 6.76 (s, 1H), 3.62 (m, 2H), 3.48 (m, 3H), 1.80 (m, 2H), 1.03 (d, 6H).
A-284	DMSO-d <sup>6</sup>	13.40 (s, 1H), 12.59 (s, 1H), 8.88 (d, 1H), 8.00 (m, 2H), 7.72 (s, 1H), 7.60 (d, 1H), 7.47 (m, 2H), 6.80 (s, 1H), 4.63 (m, 1H), 2.40 (m, 2H), 2.00 (m, 2H), 1.76 (m, 2H).
A-285	DMSO-d <sup>6</sup>	13.40 (s, 1H), 12.64 (s, 1H), 8.68 (d, 1H), 7.98 (m, 2H), 7.70 (s, 1H), 7.60 (d, 1H), 7.48 (m, 2H), 6.78 (s, 1H), 4.28 (m, 1H), 1.60 (m, 2H), 1.23 (d, 3H), 0.95 (t, 3H).
A-286	DMSO-d <sup>6</sup>	13.40 (s, 1H), 12.62 (s, 1H), 8.63 (d, 1H), 7.99 (m, 2H), 7.70 (s, 1H), 7.61 (d, 1H), 7.48 (m, 2H), 6.77 (s, 1H), 4.40 (m, 1H), 1.27 (d, 6H).
A-287	DMSO-d <sup>6</sup>	13.38 (s, 1H), 12.62 (s, 1H), 8.80 (t, 1H), 8.00 (m, 2H), 7.72 (s, 1H), 7.61 (d, 1H), 7.48 (m, 2H), 6.80 (s, 1H), 3.45 (t, 2H), 1.92 (m, 1H), 0.97 (d, 6H).

TABLE 3-continued

Compound No.	NMR Solvent	<sup>1</sup> H NMR Resonance Data (δ)
A-288	DMSO-d <sup>6</sup>	13.40 (s, 1H), 12.79 (s, 1H), 8.95 (s, 1H), 7.97 (m, 2H), 7.72 (s, 1H), 7.61 (d, 1H), 7.48 (m, 2H), 6.78 (s, 1H), 2.19 (m, 2H), 1.75 (m, 6H), 1.60 (s, 3H).
A-289	DMSO-d <sup>6</sup>	13.38 (s, 1H), 12.61 (s, 1H), 8.81 (d, 1H), 8.00 (m, 2H), 7.70 (s, 1H), 7.61 (d, 1H), 7.45 (m, 2H), 6.78 (s, 1H), 4.52 (m, 1H), 2.04 (m, 2H), 1.60 (m, 6H).
A-290	DMSO-d <sup>6</sup>	13.41 (s, 1H), 12.82 (s, 1H), 8.90 (s, 1H), 7.96 (m, 2H), 7.73 (s, 1H), 7.62 (d, 1H), 7.50 (m, 2H), 6.76 (s, 1H), 4.06 (m, 1H), 3.12 (d, 3H), 1.53 (s, 9H).
A-291	DMSO-d <sup>6</sup>	13.40 (bs, 1H), 12.68 (s, 1H), 8.87 (d, 1H), 8.30 (d, 2H), 7.78 (d, 2H), 7.50 (d, 2H), 7.27 (t, 1H), 6.78 (s, 1H), 4.55 (m, 1H), 2.06 (m, 2H), 1.60 (m, 6H).
A-292	DMSO-d <sup>6</sup>	13.39 (s, 1H), 12.64 (s, 1H), 9.18 (t, 1H), 8.25 (d, 2H), 7.79 (d, 2H), 7.52 (m, 4H), 7.24 (m, 2H), 6.82 (s, 1H), 4.85 (d, 2H).
A-293	DMSO-d <sup>6</sup>	13.40 (s, 1H), 12.70 (s, 1H), 8.85 (t, 1H), 8.30 (d, 2H), 7.80 (d, 2H), 7.53 (d, 2H), 7.28 (t, 1H), 6.79 (s, 1H), 3.45 (t, 2H), 1.95 (m, 1H), 0.97 (d, 6H).
A-296	DMSO-d <sup>6</sup>	13.41 (s, 1H), 12.70 (s, 1H), 8.69 (d, 1H), 8.30 (d, 2H), 7.80 (d, 2H), 7.50 (d, 2H), 7.28 (t, 1H), 6.78 (s, 1H), 4.40 (m, 1H), 1.27 (d, 6H).
A-297	DMSO-d <sup>6</sup>	13.41 (s, 1H), 12.73 (s, 1H), 8.72 (d, 1H), 8.28 (d, 2H), 7.79 (d, 2H), 7.51 (d, 2H), 7.28 (t, 1H), 6.78 (s, 1H), 4.30 (m, 1H), 1.61 (m, 2H), 1.23 (d, 3H), 0.95 (t, 3H).
A-298	DMSO-d <sup>6</sup>	13.40 (s, 1H), 12.63 (s, 1H), 8.93 (d, 1H), 8.30 (d, 2H), 7.80 (d, 2H), 7.50 (d, 2H), 7.28 (t, 1H), 6.80 (s, 1H), 4.63 (m, 1H), 2.40 (m, 2H), 2.00 (m, 2H), 1.75 (m, 2H).
A-299	DMSO-d <sup>6</sup>	13.42 (s, 1H), 12.90 (s, 1H), 8.92 (s, 1H), 8.28 (d, 2H), 7.82 (d, 2H), 7.53 (d, 2H), 7.28 (t, 1H), 6.78 (s, 1H), 1.55 (s, 9H).
A-300	DMSO-d <sup>6</sup>	13.26 (s, 1H), 12.60 (s, 1H), 8.95 (t, 1H), 8.40 (m, 2H), 7.96 (d, 1H), 7.78 (d, 2H), 7.65 (t, 1H), 7.55 (d, 2H), 6.63 (s, 1H), 3.60 (m, 1H), 3.41 (m, 1H), 1.71 (m, 1H), 1.43 (m, 1H), 1.22 (m, 1H), 0.94 (m, 6H).
A-301	DMSO-d <sup>6</sup>	13.21 (s, 1H), 12.56 (s, 1H), 8.79 (t, 1H), 8.41 (m, 2H), 7.95 (d, 1H), 7.78 (d, 2H), 7.64 (t, 1H), 7.54 (d, 2H), 6.63 (s, 1H), 3.65 (m, 2H), 3.48 (m, 3H), 1.80 (m, 2H), 1.05 (d, 6H).
A-302	DMSO-d <sup>6</sup>	13.29 (s, 1H), 12.58 (s, 1H), 8.97 (d, 1H), 8.41 (s, 2H), 7.95 (d, 1H), 7.76 (d, 2H), 7.65 (d, 1H), 7.52 (d, 2H), 6.63 (s, 1H), 4.57 (m, 1H), 2.06 (m, 2H), 1.62 (m, 6H).
A-303	DMSO-d <sup>6</sup>	13.28 (s, 1H), 12.60 (s, 1H), 8.94 (t, 1H), 8.40 (m, 2H), 7.95 (d, 1H), 7.77 (d, 2H), 7.65 (t, 1H), 7.54 (d, 2H), 6.65 (s, 1H), 3.45 (t, 2H), 1.93 (m, 1H), 0.98 (d, 6H).
A-304	DMSO-d <sup>6</sup>	13.30 (s, 1H), 12.62 (s, 1H), 8.94 (d, 1H), 8.40 (m, 2H), 7.95 (d, 1H), 7.77 (d, 2H), 7.65 (t, 1H), 7.53 (d, 2H), 6.64 (s, 1H), 4.30 (m, 1H), 1.90 (m, 1H), 1.20 (d, 3H), 0.95 (m, 6H).
A-305	DMSO-d <sup>6</sup>	13.30 (s, 1H), 12.59 (s, 1H), 8.80 (d, 1H), 8.40 (m, 2H), 7.97 (d, 1H), 7.76 (d, 2H), 7.66 (t, 1H), 7.54 (d, 2H), 6.63 (s, 1H), 4.42 (m, 1H), 1.27 (d, 6H).
A-306	DMSO-d <sup>6</sup>	13.31 (s, 1H), 12.61 (s, 1H), 8.80 (d, 1H), 8.40 (m, 2H), 7.96 (d, 1H), 7.76 (d, 2H), 7.65 (t, 1H), 7.53 (d, 2H), 6.64 (s, 1H), 4.31 (m, 1H), 1.62 (m, 2H), 1.23 (d, 3H), 0.96 (t, 3H).
A-307	DMSO-d <sup>6</sup>	13.32 (s, 1H), 12.53 (s, 1H), 9.02 (d, 1H), 8.40 (m, 2H), 7.95 (d, 1H), 7.75 (d, 2H), 7.65 (t, 1H), 7.52 (d, 2H), 6.64 (s, 1H), 4.65 (m, 1H), 2.40 (m, 2H), 2.00 (m, 2H), 1.75 (m, 2H).
A-308	DMSO-d <sup>6</sup>	13.32 (s, 1H), 12.78 (s, 1H), 9.00 (s, 1H), 8.40 (m, 2H), 7.98 (d, 1H), 7.78 (d, 2H), 7.70 (t, 1H), 7.53 (d, 2H), 6.63 (s, 1H), 1.54 (s, 9H).
A-309	DMSO-d <sup>6</sup>	13.40 (bs, 1H), 12.62 (s, 1H), 8.89 (d, 1H), 8.40 (m, 2H), 7.95 (d, 1H), 7.66 (t, 1H), 7.50 (d, 2H), 7.28 (t, 1H), 6.78 (s, 1H), 4.58 (m, 1H), 2.05 (m, 2H), 1.60 (m, 6H).
A-310	DMSO-d <sup>6</sup>	13.39 (bs, 1H), 12.62 (s, 1H), 8.85 (t, 1H), 8.40 (m, 2H), 7.96 (d, 1H), 7.65 (t, 1H), 7.52 (d, 2H), 7.26 (t, 1H), 6.79 (s, 1H), 3.45 (t, 2H), 1.92 (m, 1H), 0.95 (d, 6H).
A-311	DMSO-d <sup>6</sup>	13.42 (s, 1H), 12.69 (s, 1H), 8.83 (d, 1H), 8.40 (m, 2H), 7.98 (d, 1H), 7.65 (d, 1H), 7.52 (d, 2H), 7.28 (t, 1H), 6.79 (s, 1H), 4.31 (m, 1H), 1.90 (m, 1H), 1.20 (d, 1H), 0.95 (m, 6H).
A-313	DMSO-d <sup>6</sup>	13.40 (s, 1H), 12.63 (s, 1H), 8.73 (d, 1H), 8.40 (m, 2H), 7.97 (d, 1H), 7.64 (t, 1H), 7.50 (d, 2H), 7.26 (t, 1H), 6.78 (s, 1H), 4.30 (m, 1H), 1.60 (m, 2H), 1.23 (d, 3H), 0.94 (t, 3H).
A-314	DMSO-d <sup>6</sup>	13.42 (bs, 1H), 12.59 (s, 1H), 8.96 (d, 1H), 8.40 (m, 2H), 7.96 (d, 1H), 7.65 (t, 1H), 7.50 (d, 2H), 7.29 (t, 1H), 6.79 (s, 1H), 4.66 (m, 1H), 2.40 (m, 2H), 2.00 (m, 2H), 1.75 (m, 2H).
A-319	DMSO-d <sup>6</sup>	13.24 (s, 1H), 12.60 (s, 1H), 8.78 (d, 1H), 8.00 (m, 2H), 7.53 (m, 3H), 7.40 (m, 1H), 6.63 (s, 1H), 4.41 (m, 1H), 3.14 (s, 2H), 2.22 (s, 3H), 1.26 (d, 6H).
A-323	DMSO-d <sup>6</sup>	13.22 (s, 1H), 12.62 (s, 1H), 8.90 (t, 1H), 8.00 (m, 2H), 7.52 (m, 3H), 7.40 (m, 1H), 6.63 (s, 1H), 3.45 (t, 2H), 2.22 (s, 3H), 1.93 (m, 1H), 0.98 (d, 6H).
A-335	DMSO-d <sup>6</sup>	12.80 (s, 1H), 12.53 (s, 1H), 8.80 (t, 1H), 8.28 (d, 2H), 7.80 (d, 2H), 7.52 (m, 2H), 7.22 (t, 1H), 4.84 (d, 2H), 1.30 (s, 9H).

TABLE 3-continued

Compound No.	NMR Solvent	<sup>1</sup> H NMR Resonance Data (δ)
A-338	DMSO-d <sup>6</sup>	14.0 (s, 1H), 12.46 (s, 1H), 9.01 (t, 1H), 8.23 (d, 2H), 7.79 (d, 2H), 7.50 (m, 2H), 7.21 (m, 1H), 6.80 (s, 1H), 4.82 (d, 2H), 3.82 (s, 3H).
A-339	DMSO-d <sup>6</sup>	13.93 (s, 1H), 12.69 (s, 1H), 8.80 (s, 1H), 8.28 (d, 2H), 7.83 (d, 2H), 6.74 (s, 1H), 3.82 (s, 3H), 1.53 (s, 9H).
A-340	DMSO-d <sup>6</sup>	13.08 (s, 1H), 12.58 (s, 1H), 8.60 (s, 1H), 8.48 (d, 2H), 7.82 (d, 2H), 1.57 (s, 9H), 1.30 (s, 9H).
A-346	DMSO-d <sup>6</sup>	13.39 (s, 1H), 12.62 (s, 1H), 8.83 (s, 1H), 7.99 (d, 2H), 7.69 (d, 1H), 7.53 (d, 2H), 7.30 (t, 1H), 6.80 (s, 1H), 3.60 (m, 1H), 3.45 (m, 1H), 1.70 (m, 1H), 1.45 (m, 1H), 0.94 (m, 6H).
A-347	DMSO-d <sup>6</sup>	13.42 (bs, 1H), 12.59 (s, 1H), 8.94 (d, 1H), 7.99 (d, 2H), 7.66 (d, 1H), 7.53 (d, 2H), 7.28 (t, 1H), 6.80 (s, 1H), 4.65 (m, 1H), 2.40 (m, 2H), 2.00 (m, 2H), 1.78 (m, 2H).
A-351	DMSO-d <sup>6</sup>	13.42 (s, 1H), 12.70 (s, 1H), 8.82 (d, 1H), 7.98 (d, 2H), 7.69 (t, 1H), 7.52 (d, 2H), 7.30 (t, 1H), 6.79 (s, 1H), 4.30 (t, 1H), 1.90 (m, 1H), 1.20 (d, 3H), 0.99 (m, 6H).
A-352	DMSO-d <sup>6</sup>	13.38 (s, 1H), 12.62 (s, 1H), 8.84 (t, 1H), 7.95 (d, 2H), 7.65 (m, 1H), 7.53 (m, 2H), 7.28 (t, 1H), 6.79 (s, 1H), 3.44 (m, 2H), 1.92 (m, 1H), 0.96 (d, 6H).
A-356	DMSO-d <sup>6</sup>	13.41 (s, 1H), 12.63 (s, 1H), 8.71 (d, 1H), 7.95 (m, 2H), 7.66 (m, 1H), 7.52 (m, 2H), 7.28 (t, 1H), 6.78 (s, 1H), 4.28 (m, 1H), 1.60 (m, 2H), 1.22 (d, 3H), 0.98 (t, 3H).
A-362	DMSO-d <sup>6</sup>	13.41 (s, 1H), 12.63 (s, 1H), 8.70 (d, 1H), 7.94 (m, 2H), 7.65 (m, 1H), 7.52 (d, 2H), 7.28 (t, 1H), 6.77 (s, 1H), 4.28 (m, 1H), 1.60 (m, 2H), 1.22 (d, 3H), 0.93 (t, 3H).
A-363	DMSO-d <sup>6</sup>	13.40 (s, 1H), 12.69 (s, 1H), 8.88 (d, 1H), 8.00 (m, 2H), 7.50 (m, 3H), 7.28 (t, 1H), 6.75 (s, 1H), 4.55 (m, 1H), 3.47 (d, 2H), 3.30 (s, 3H), 1.26 (d, 3H).
A-364	DMSO-d <sup>6</sup>	13.38 (s, 1H), 12.64 (s, 1H), 8.81 (t, 1H), 8.00 (m, 2H), 7.52 (m, 3H), 7.28 (t, 1H), 6.78 (s, 1H), 3.45 (m, 2H), 1.92 (m, 1H), 0.97 (d, 6H).
A-365	DMSO-d <sup>6</sup>	13.40 (s, 1H), 12.63 (s, 1H), 8.82 (d, 1H), 8.00 (m, 2H), 7.50 (m, 3H), 7.28 (t, 1H), 6.75 (s, 1H), 4.53 (t, 1H), 4.07 (m, 1H), 3.14 (m, 2H), 2.06 (m, 2H), 1.61 (m, 6H).
A-366	DMSO-d <sup>6</sup>	13.40 (s, 1H), 12.63 (s, 1H), 8.66 (d, 1H), 8.00 (m, 2H), 7.50 (m, 3H), 7.28 (t, 1H), 6.74 (s, 1H), 4.40 (m, 1H), 4.07 (m, 1H), 3.14 (m, 4H), 1.25 (d, 6H).
A-369	DMSO-d <sup>6</sup>	13.40 (s, 1H), 12.72 (s, 1H), 8.81 (d, 1H), 8.00 (d, 1H), 7.80 (d, 1H), 7.50 (m, 3H), 7.30 (m, 2H), 6.76 (s, 1H), 4.53 (m, 1H), 2.04 (m, 2H), 1.60 (m, 6H).
A-370	DMSO-d <sup>6</sup>	13.40 (s, 1H), 12.74 (s, 1H), 8.65 (d, 1H), 7.98 (d, 1H), 7.80 (d, 1H), 7.50 (m, 3H), 7.30 (m, 2H), 6.78 (s, 1H), 4.40 (m, 1H), 1.30 (d, 6H).
A-375	DMSO-d <sup>6</sup>	13.24 (s, 1H), 12.84 (s, 1H), 8.98 (s, 1H), 8.21 (d, 2H), 7.83 (d, 2H), 7.80 (t, 2H), 7.30 (t, 2H), 6.60 (s, 1H), 3.13 (s, 3H), 2.89 (s, 3H), 1.55 (s, 9H).
A-376	DMSO-d <sup>6</sup>	13.30 (s, 1H), 12.63 (s, 1H), 8.94 (d, 1H), 7.98 (m, 2H), 7.74 (d, 2H), 7.50 (m, 3H), 6.62 (s, 1H), 4.55 (m, 1H), 4.05 (t, 1H), 3.47 (s, 2H), 3.30 (s, 3H), 3.12 (d, 2H), 1.23 (d, 3H).
A-377	DMSO-d <sup>6</sup>	13.27 (s, 1H), 12.59 (s, 1H), 8.89 (t, 1H), 7.99 (m, 2H), 7.77 (d, 2H), 7.50 (m, 3H), 6.63 (s, 1H), 3.45 (m, 2H), 1.90 (m, 1H), 0.95 (d, 6H).
A-378	DMSO-d <sup>6</sup>	13.28 (s, 1H), 12.59 (s, 1H), 8.91 (d, 1H), 8.00 (m, 2H), 7.75 (d, 2H), 7.49 (m, 3H), 6.62 (s, 1H), 4.52 (m, 1H), 2.05 (m, 2H), 1.60 (m, 6H).
A-379	DMSO-d <sup>6</sup>	13.28 (s, 1H), 12.59 (s, 1H), 8.75 (d, 1H), 8.00 (m, 2H), 7.75 (d, 2H), 7.50 (m, 3H), 6.62 (s, 1H), 4.40 (m, 1H), 1.25 (d, 6H).
A-380	DMSO-d <sup>6</sup>	13.30 (s, 1H), 12.61 (s, 1H), 8.98 (d, 1H), 7.96 (m, 2H), 7.76 (d, 2H), 7.65 (t, 1H), 7.52 (d, 2H), 6.62 (s, 1H), 4.55 (m, 1H), 3.46 (m, 2H), 3.30 (s, 3H), 3.12 (s, 2H), 1.24 (d, 3H).
A-381	DMSO-d <sup>6</sup>	13.24 (s, 1H), 12.58 (s, 1H), 8.92 (t, 1H), 7.95 (m, 2H), 7.76 (d, 2H), 7.65 (t, 1H), 7.54 (d, 2H), 6.65 (s, 1H), 3.43 (m, 2H), 1.92 (m, 1H), 0.95 (d, 6H).
A-382	DMSO-d <sup>6</sup>	13.27 (s, 1H), 12.56 (s, 1H), 8.95 (d, 1H), 7.96 (m, 2H), 7.74 (d, 2H), 7.62 (t, 1H), 7.53 (d, 2H), 6.62 (s, 1H), 4.52 (m, 1H), 2.03 (m, 2H), 1.60 (m, 6H).
A-383	DMSO-d <sup>6</sup>	13.28 (s, 1H), 12.58 (s, 1H), 8.78 (d, 1H), 7.96 (m, 2H), 7.74 (d, 2H), 7.64 (t, 1H), 7.53 (d, 2H), 6.62 (s, 1H), 4.40 (m, 1H), 1.26 (d, 6H).
A-385	DMSO-d <sup>6</sup>	13.28 (s, 1H), 12.62 (s, 1H), 8.89 (d, 1H), 7.99 (d, 1H), 7.80 (m, 1H), 7.75 (d, 2H), 7.52 (d, 2H), 7.47 (m, 1H), 7.32 (t, 1H), 6.62 (s, 1H), 4.53 (m, 1H), 2.07 (m, 2H), 1.60 (m, 6H).
A-386	DMSO-d <sup>6</sup>	13.28 (s, 1H), 12.65 (s, 1H), 8.72 (d, 1H), 7.95 (m, 1H), 7.80 (m, 1H), 7.75 (d, 2H), 7.55 (d, 2H), 7.48 (m, 1H), 7.32 (m, 1H), 6.62 (s, 1H), 4.40 (m, 1H), 1.27 (d, 6H).
A-396	DMSO-d <sup>6</sup>	13.18 (s, 1H), 12.43 (s, 1H), 9.19 (t, 1H), 7.86 (m, 2H), 7.78 (m, 2H), 7.28 (m, 3H), 6.98 (m, 2H), 6.82 (m, 1H), 6.60 (s, 1H), 4.78 (s, 2H), 3.70 (s, 3H).
A-398	DMSO-d <sup>6</sup>	13.14 (s, 1H), 12.64 (s, 1H), 9.11 (t, 1H), 7.96 (m, 1H), 7.80 (m, 3H), 7.45 (m, 1H), 7.28 (m, 4H), 7.00 (m, 2H), 6.82 (m, 1H), 6.61 (s, 1H), 4.78 (d, 2H), 3.69 (s, 3H).

TABLE 3-continued

Compound No.	NMR Solvent	<sup>1</sup> H NMR Resonance Data (δ)
A-399	DMSO-d <sup>6</sup>	13.15 (s, 1H), 12.69 (s, 1H), 9.05 (t, 1H), 7.98 (m, 1H), 7.80 (m, 3H), 7.47 (m, 1H), 7.32 (m, 4H), 7.19 (m, 3H), 6.61 (s, 1H), 4.81 (m, 2H), 2.37 (s, 3H).
A-403	DMSO-d <sup>6</sup>	13.28 (s, 1H), 12.62 (s, 1H), 9.03 (s, 1H), 7.80 (m, 4H), 7.30 (m, 2H), 6.60 (s, 1H), 1.71 (s, 9H).
A-418	DMSO-d <sup>6</sup>	13.19 (s, 1H), 12.92 (s, 1H), 8.90 (s, 1H), 8.14 (m, 2H), 7.70 (m, 1H), 7.60 (m, 1H), 7.25 (m, 3H), 6.51 (s, 1H), 2.24 (s, 3H), 1.55 (s, 9H).
A-420	DMSO-d <sup>6</sup>	13.42 (s, 1H), 12.85 (s, 1H), 8.90 (s, 1H), 7.97 (m, 2H), 7.52 (m, 3H), 7.29 (m, 1H), 6.73 (s, 1H), 1.52 (s, 9H).
A-421	DMSO-d <sup>6</sup>	13.44 (s, 1H), 12.70 (s, 1H), 8.97 (d, 1H), 8.35 (m, 2H), 8.15 (m, 1H), 8.07 (m, 1H), 7.91 (m, 2H), 7.74 (m, 2H), 6.82 (s, 1H), 4.59 (m, 1H), 2.09 (m, 2H), 1.62 (m, 6H).
A-423	DMSO-d <sup>6</sup>	13.45 (s, 1H), 12.82 (s, 1H), 8.97 (s, 1H), 8.13 (s, 1H), 8.03 (m, 1H), 7.96 (m, 2H), 7.70 (m, 2H), 7.52 (m, 1H), 6.79 (s, 1H), 1.52 (s, 9H).
A-429	DMSO-d <sup>6</sup>	13.2 (s, 1H), 12.6 (s, 1H), 9.0 (t, 1H), 8.6 (s, 1H), 8.4 (d, 1H), 8.0 (d, 1H), 7.8 (dd, 1H), 7.7 (dd, 2H), 7.3 (dd, 2H), 6.6 (s, 1H), 3.5 (dd, 2H), 3.2 (s, 3H), 1.9 (m, 1H), 0.99 (s, 3H), 0.98 (s, 3H).
A-430	DMSO-d <sup>6</sup>	13.3 (s, 1H), 12.6 (s, 1H), 8.8 (d, 1H), 8.6 (s, 1H), 8.4 (d, 1H), 8.0 (d, 1H), 7.8 (dd, 1H), 7.7 (dd, 2H), 7.3 (dd, 2H), 6.6 (s, 1H), 4.3 (m, 1H), 3.2 (s, 3H), 1.6 (m, 2H), 1.27 (d, 3H), 0.97 (t, 3H).
A-485	DMSO-d <sup>6</sup>	13.26 (s, 1H), 12.75 (s, 1H), 10.52 (s, 1H), 9.01 (s, 1H), 8.80 (s, 1H), 8.38 (m, 1H), 7.78 (m, 2H), 7.63 (m, 1H), 7.32 (m, 2H), 6.59 (s, 1H), 2.09 (s, 3H), 1.56 (s, 9H).
A-486	DMSO-d <sup>6</sup>	13.31 (s, 1H), 12.54 (s, 1H), 9.15 (s, 1H), 8.01 (m, 1H), 7.86 (s, 2H), 7.79 (m, 2H), 7.48 (m, 1H), 7.32 (m, 2H), 7.26 (m, 1H), 6.61 (s, 1H), 1.54 (s, 9H).
A-487	DMSO-d <sup>6</sup>	13.24 (s, 1H), 12.80 (s, 1H), 8.94 (s, 1H), 8.14 (m, 1H), 7.78 (m, 2H), 7.33 (m, 2H), 7.10 (m, 2H), 6.56 (s, 1H), 3.39 (m, 4H), 1.96 (m, 4H), 1.55 (s, 9H).
A-488	DMSO-d <sup>6</sup>	13.22 (s, 1H), 12.56 (s, 1H), 8.93 (m, 1H), 8.03 (m, 1H), 7.78 (m, 2H), 7.32 (m, 2H), 7.21 (m, 1H), 7.10 (m, 1H), 6.60 (s, 1H), 4.45 (m, 1H), 3.45 (m, 2H), 3.3 (s, 3H), 1.23 (m, 3H).
A-489	DMSO-d <sup>6</sup>	13.23 (s, 1H), 12.74 (s, 1H), 8.94 (s, 1H), 8.02 (m, 1H), 7.78 (m, 2H), 7.33 (m, 2H), 7.24 (m, 1H), 7.15 (m, 1H), 6.58 (s, 1H), 1.50 (s, 9H).
A-490	DMSO-d <sup>6</sup>	13.29 (s, 1H), 12.75 (s, 1H), 8.89 (m, 1H), 8.18 (m, 2H), 7.79 (m, 2H), 7.33 (m, 2H), 7.25 (m, 2H).
A-491	DMSO-d <sup>6</sup>	13.25 (s, 1H), 12.66 (s, 1H), 9.01 (m, 1H), 8.59 (s, 1H), 8.43 (m, 1H), 8.05 (m, 1H), 7.8 (m, 2H), 7.73 (m, 1H), 7.33 (m, 2H), 6.61 (s, 1H), 4.57 (m, 1H), 3.51 (m, 2H), 3.33 (s, 3H), 3.23 (s, 3H), 1.28 (m, 3H).
A-492	DMSO-d <sup>6</sup>	13.16 (s, 1H), 12.95 (s, 1H), 9.90 (s, 1H), 8.75 (m, 1H), 7.98 (m, 2H), 7.78 (m, 2H), 7.32 (m, 2H), 6.76 (m, 2H), 6.55 (s, 1H), 4.53 (m, 1H), 3.47 (m, 2H), 3.31 (s, 3H), 1.25 (m, 3H).
A-493	DMSO-d <sup>6</sup>	13.21 (s, 1H), 12.72 (s, 1H), 8.91 (m, 2H), 8.29 (m, 1H), 7.78 (m, 2H), 7.32 (m, 2H), 6.84 (m, 1H), 6.58 (s, 1H), 4.55 (m, 1H), 3.89 (s, 3H), 3.48 (m, 2H), 1.26 (m, 3H).
A-494	DMSO-d <sup>6</sup>	13.23 (s, 1H), 12.87 (s, 1H), 8.90 (m, 2H), 8.26 (m, 1H), 7.78 (m, 2H), 7.32 (m, 2H), 6.88 (m, 1H), 6.56 (s, 1H), 3.90 (s, 3H), 1.55 (s, 9H).
A-495	DMSO-d <sup>6</sup>	13.25 (s, 1H), 12.60 (s, 1H), 9.02 (m, 1H), 8.24 (m, 1H), 7.79 (m, 2H), 7.55 (m, 1H), 7.35 (m, 3H), 6.61 (s, 1H), 4.55 (m, 1H), 3.87 (s, 3H), 3.48 (m, 2H), 1.26 (m, 3H).
A-496	DMSO-d <sup>6</sup>	13.27 (s, 1H), 12.73 (s, 1H), 9.03 (s, 1H), 8.27 (m, 1H), 7.78 (m, 2H), 7.54 (m, 1H), 7.34 (m, 3H), 6.60 (s, 1H), 3.87 (s, 3H), 1.55 (s, 9H).
A-497	DMSO-d <sup>6</sup>	13.25 (s, 1H), 12.68 (s, 1H), 9.01 (m, 1H), 8.32 (m, 2H), 7.98 (m, 2H), 7.79 (m, 2H), 7.33 (m, 2H), 6.62 (s, 1H), 4.58 (m, 1H), 3.49 (m, 2H), 3.33 (s, 3H), 3.23 (s, 1H), 1.27 (m, 3H).
A-498	DMSO-d <sup>6</sup>	13.26 (s, 1H), 12.81 (s, 1H), 9.03 (s, 1H), 8.30 (m, 2H), 8.01 (m, 2H), 7.79 (m, 2H), 7.32 (m, 2H), 6.61 (s, 1H), 3.23 (s, 3H), 1.57 (s, 9H).
A-499	DMSO-d <sup>6</sup>	13.26 (s, 1H), 12.78 (s, 1H), 9.02 (s, 1H), 8.63 (s, 1H), 8.42 (m, 1H), 8.06 (m, 1H), 7.8 (m, 3H), 7.32 (m, 2H), 6.60 (s, 1H), 3.23 (s, 3H), 1.57 (s, 9H).
A-500	DMSO-d <sup>6</sup>	13.20 (s, 1H), 12.78 (s, 1H), 8.90 (m, 1H), 8.17 (m, 2H), 7.78 (m, 2H), 7.32 (m, 2H), 7.24 (m, 2H), 6.59 (s, 1H), 4.55 (m, 1H), 3.48 (m, 2H), 3.32 (s, 3H), 1.26 (m, 3H).
A-533	DMSO-d <sup>6</sup>	13.21 (s, 1H), 12.78 (s, 1H), 8.90 (m, 1H), 8.17 (m, 2H), 7.78 (m, 2H), 7.32 (m, 2H), 7.24 (m, 2H), 6.59 (s, 1H), 4.56 (m, 1H), 3.48 (m, 2H), 3.32 (s, 3H), 1.27 (m, 3H).
A-538	DMSO-d <sup>6</sup>	13.21 (s, 1H), 12.97 (s, 1H), 8.92 (s, 1H), 8.14 (m, 2H), 7.79 (m, 2H), 7.31 (m, 4H), 6.56 (s, 1H), 3.62 (m, 2H), 1.48 (s, 6H).
A-539	DMSO-d <sup>6</sup>	13.19 (s, 1H), 13.06 (s, 1H), 8.81 (s, 1H), 8.07 (m, 2H), 7.78 (m, 2H), 7.32 (m, 2H), 6.98 (m, 2H), 6.54 (s, 1H), 3.79 (s, 3H), 1.55 (s, 9H).
A-540	DMSO-d <sup>6</sup>	13.22 (s, 1H), 12.96 (s, 1H), 8.88 (s, 1H), 7.78 (m, 2H), 7.69 (m, 2H), 7.36 (m, 3H), 7.06 (m, 1H), 6.56 (s, 1H), 3.78 (s, 3H), 1.56 (s, 9H).
A-543	DMSO-d <sup>6</sup>	12.93 (s, 1H), 10.38 (s, 1H), 8.92 (m, 1H), 7.97 (m, 1H), 7.60 (m, 1H), 7.53 (m, 1H), 7.44 (m, 1H), 7.2 (m, 2H), 7.15 (m, 1H), 6.18 (s, 1H), 4.59 (m, 2H), 3.64 (s, 3H).

TABLE 3-continued

Compound No.	NMR Solvent	<sup>1</sup> H NMR Resonance Data (δ)
A-550	DMSO-d <sub>6</sub>	13.20 (s, 1H), 13.04 (s, 1H), 8.85 (s, 1H), 8.01 (m, 2H), 7.79 (m, 2H), 7.33 (m, 2H), 7.25 (m, 2H), 6.56 (s, 1H), 2.34 (s, 3H), 1.55 (s, 9H).
A-552	DMSO-d <sub>6</sub>	13.21 (s, 1H), 13.02 (s, 1H), 8.87 (s, 1H), 7.93 (m, 2H), 7.80 (m, 2H), 7.32 (m, 4H), 6.56 (s, 1H), 2.35 (s, 3H), 1.56 (s, 9H).
A-554	DMSO-d <sub>6</sub>	13.22 (s, 1H), 12.89 (s, 1H), 8.92 (s, 1H), 7.85-7.71 (m, 4H), 7.35 (m, 3H), 6.57 (s, 1H), 2.27 (s, 3H), 1.55 (s, 9H).
A-556	DMSO-d <sub>6</sub>	13.21 (s, 1H), 12.94 (s, 1H), 8.89 (s, 1H), 8.0 (m, 2H), 7.79 (m, 2H), 7.31 (m, 2H), 7.21 (m, 1H), 6.56 (s, 1H), 2.27 (s, 3H), 1.55 (s, 9H).

## Example 6

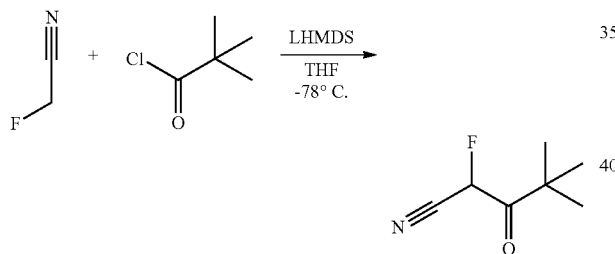
## Preparation of Exemplary Substituted Pyrazole Compounds

The substituted pyrazole compounds 3-(tert-Butyl)-4-fluoro-1H-pyrazol-5-amine and 3-(3-fluoro-4-methoxyphenyl)-1H-pyrazol-5-amine were prepared according to the procedures described in Parts I and II below, respectively.

## Part I: Preparation of 3-(tert-Butyl)-4-fluoro-1H-pyrazol-5-amine

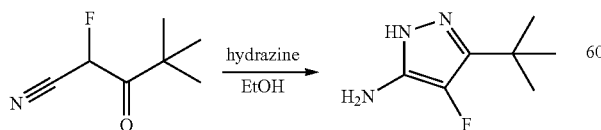
The title compound was prepared according to the procedures described below.

## Step A—Synthesis of 2-Fluoro-4,4-dimethyl-3-oxopentanenitrile



A solution of lithium hexamethyldisilazide (LHMDS) in tetrahydrofuran (THF) (1M, 33.9 mL, 2 equiv) was added dropwise to a chilled (−78° C.) solution of pivaloyl chloride (2.04 g, 1 equiv) and FCH<sub>2</sub>CN (1.00 g, 1 equiv) in THF (50 mL). The mixture was allowed to warm to room temperature and 1 N HCl was added dropwise until the solution was pH=2. The mixture was concentrated in vacuo to provide the title compound (2.40 g, 99% yield).

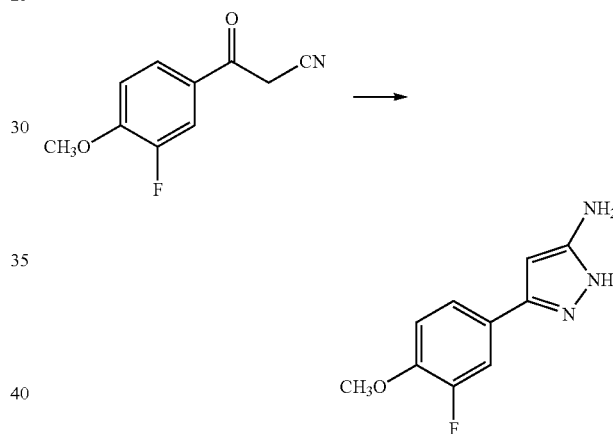
## Step B—Synthesis of 3-(tert-Butyl)-4-fluoro-1H-pyrazol-5-amine



Hydrazine (1.29 g, 2.4 equiv) was added to a solution of 2-fluoro-4,4-dimethyl-3-oxopentanenitrile (2.40 g, 1 equiv) in ethanol (EtOH) (50 mL), and the reaction was heated at

reflux overnight. The solvent was removed under reduced pressure, and the residue was dissolved in dichloromethane (DCM) and washed with water. The organic solution was dried over sodium sulfate and concentrated in vacuo to provide the title compound (1.43 g, 54% yield) which was used in the next reaction without purification.

## Part II: Preparation of 3-(3-fluoro-4-methoxyphenyl)-1H-pyrazol-5-amine



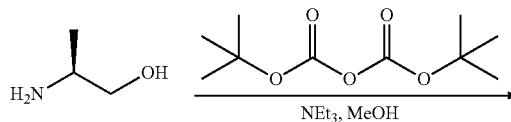
3-(3-Fluoro-4-methoxyphenyl)-3-oxopropanenitrile (2.13 g, 11 mmol) and hydrazine (0.38 mL, 12.13 mmol) were combined in absolute ethanol and the reaction mixture was heated to reflux overnight. Then, the solvent and excess hydrazine were evaporated to provide the title compound in quantitative yield.

## Example 7

## Preparation of (S)-1-Ethoxypropan-2-amine

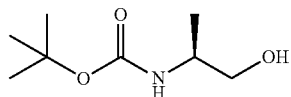
The title compound was prepared according to the procedures described below.

## Part I—Synthesis of (S)-tert-Butyl (1-hydroxypropan-2-yl)carbamate



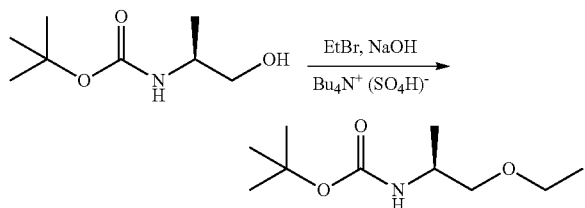
313

-continued



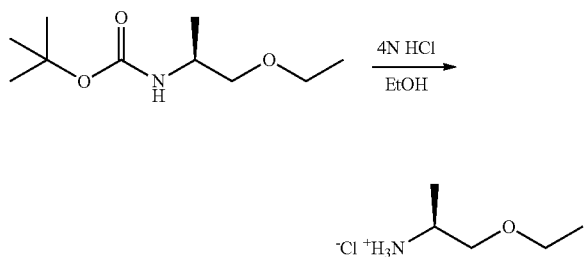
To a chilled (0° C.) solution of (S)-2-amino-1-propanol (1.28 g) and triethylamine (2.73 mL, 1.15 equiv) in methanol (MeOH) (17 mL) was added di-tert-butyl dicarbonate (4.09 g, 1.1 equiv). The reaction was stirred at room temperature overnight and then concentrated in vacuo. The residue was diluted with DCM and washed with water. The organic phase was dried over sodium sulfate and concentrated in vacuo to provide the title compound (2.89 g, 97% yield).

Part II—Synthesis of (S)-tert-Butyl  
(1-ethoxypropan-2-yl)carbamate



To a mixture of t-butyl (2-hydroxy-1-methylethyl)carbamate (2.89 g) and tetrabutylammonium hydrogen sulfate (560 mg, 0.1 equiv) in toluene (33 mL) and 50% aqueous sodium hydroxide solution (6.6 mL, 5 equiv) was added ethyl bromide (1.85 mL, 1.5 equiv) at room temperature. The mixture was stirred at room temperature for 4 days. The reaction mixture was partitioned between water and ethyl ether. The organic layer was washed with water and brine, dried over sodium sulfate, and concentrated in vacuo to provide the crude product, which was purified by silica chromatography (9:1 to 75:25 hexanes:ethyl acetate (EtOAc)) to provide the title compound (2.00 g, 60% yield).

Part III—Synthesis of (S)-1-Ethoxypropan-2-amine



(S)-tert-Butyl (1-ethoxypropan-2-yl)carbamate (2.00 g) was dissolved in a 1:1 mixture of EtOH:4N HCl in dioxane, and the reaction mixture was stirred at room temperature for 3 days. The mixture was concentrated in vacuo to provide the title compound (987 mg (impure), 97% yield).

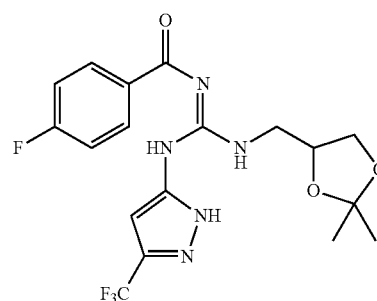
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Example 8

Preparation of (Z)—N-(((2,3-Dihydroxypropyl)amino)((3-(trifluoromethyl)-1H-pyrazol-5-yl)amino)methylene)-4-fluorobenzamide (A-562)

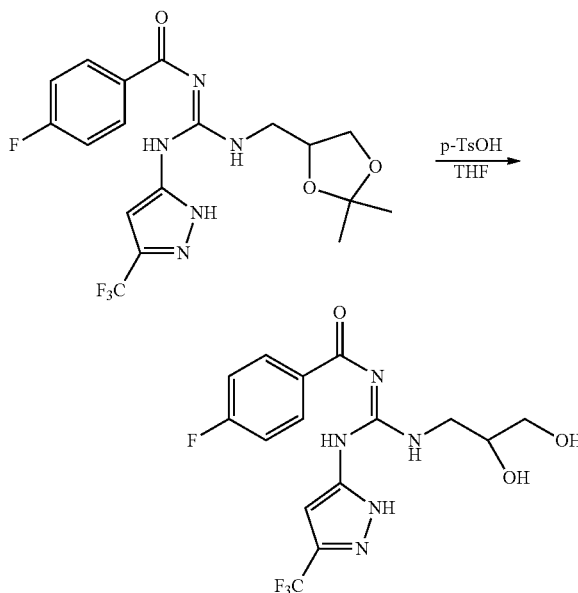
The title compound was prepared according to the procedures described below.

Part I—Synthesis of (Z)—N-(((2,2-Dimethyl-1,3-dioxolan-4-yl)methyl)amino)((3-(trifluoromethyl)-1H-pyrazol-5-yl)amino)methylene)-4-fluorobenzamide



The title compound was prepared from 4-fluorobenzoyl chloride, (2,2-dimethyl-1,3-dioxolan-4-yl)methanamine, and 3-(trifluoromethyl)-1H-pyrazol-5-amine based on synthetic procedures described in Example 4.

Part II—Synthesis of (Z)—N-(((2,3-Dihydroxypropyl)amino)((3-(trifluoromethyl)-1H-pyrazol-5-yl)amino)methylene)-4-fluorobenzamide (A-562)



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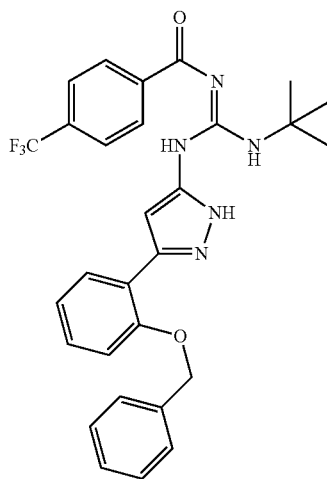
To a solution of (Z)—N-(((2,2-dimethyl-1,3-dioxolan-4-yl)methyl)amino)((3-(trifluoromethyl)-1H-pyrazol-5-yl)amino)methylene)-4-fluorobenzamide (300 mg) in THF (7 mL) was added para-toluenesulfonic acid (p-TsOH) (133 mg, 1 equiv). The reaction mixture was shaken at room temperature overnight. The solution was then treated with triethylamine (100  $\mu$ L), concentrated onto silica gel, and purified by silica chromatography (3:1 hexanes:EtOAc to EtOAc) to provide the title compound (115 mg (91% purity), 42% yield). MS (EI+) m/z: 389.93, 411.89; HPLC (Method B): 5.19 min

## Example 9

Preparation of (Z)—N-((tert-Butylamino)((3-(2-hydroxyphenyl)-1H-pyrazol-5-yl)amino)methylene)-4-(trifluoromethyl)benzamide (A-563)

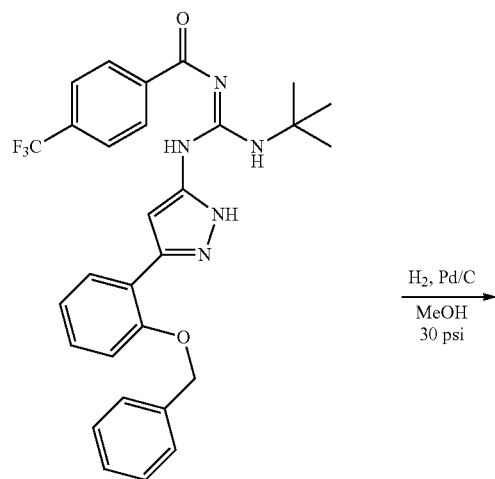
The title compound was prepared according to the procedures described below.

Part I—Synthesis of (Z)—N-(((3-(2-(Benzyloxy)phenyl)-1H-pyrazol-5-yl)amino)(tert-butylamino)methylene)-4-(trifluoromethyl)benzamide



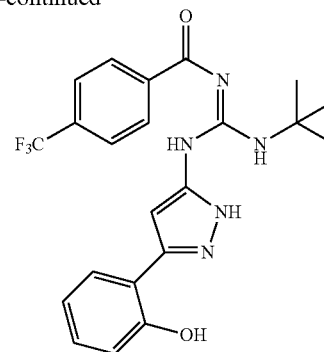
The title compound was prepared from 4-(trifluoromethyl)benzoyl chloride, 2-methylpropan-2-amine, and 3-(2-(benzyloxy)phenyl)-1H-pyrazol-5-amine based on synthetic procedures described in Example 4.

Part II—Synthesis of (Z)—N-((tert-Butylamino)((3-(2-hydroxyphenyl)-1H-pyrazol-5-yl)amino)methylene)-4-(trifluoromethyl)benzamide (A-563)



## 316

-continued



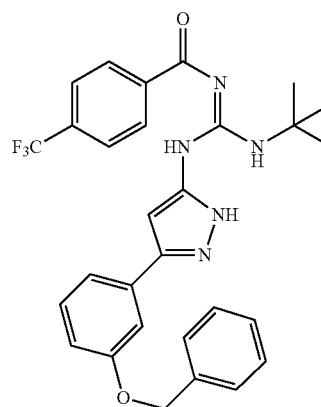
(Z)—N-(((3-(2-(Benzyloxy)phenyl)-1H-pyrazol-5-yl)amino)(tert-butylamino)methylene)-4-(trifluoromethyl)benzamide (190 mg) was dissolved in methanol (10 mL) and the solution was degassed with nitrogen. To the solution was added 10% palladium on carbon (38 mg, 0.1 equiv). The resulting mixture was subjected to hydrogen gas at 30 psi pressure in a Parr shaker. The reaction was checked periodically for completion. Upon reaction completion, the mixture was filtered through celite, and the filtrate was concentrated in vacuo to provide the crude product, which was purified by silica chromatography (9:1 to 55:45 hexanes:EtOAc) to provide the title compound (69 mg, 44% yield). <sup>1</sup>HNMR (400 MHz, DMSO-d<sub>6</sub>)  $\delta$  12.79 (bm, 2H), 10.32 (bs, 1H), 9.05 (s, 1H), 8.28 (d, 2H), 7.82 (d, 2H), 7.61 (d, 1H), 7.19 (t, 1H), 6.95 (d, 1H), 6.86 (t, 1H), 6.53 (s, 1H), 4.06 (m, 1H), 3.14 (s, 1H), 1.56 (s, 9H); MS (EI+) m/z: 446.00, 467.97; HPLC (Method B): 6.15 min

## Example 10

Preparation of (Z)—N-((tert-Butylamino)((3-(3-hydroxyphenyl)-1H-pyrazol-5-yl)amino)methylene)-4-(trifluoromethyl)benzamide (A-564)

The title compound was prepared according to the procedures described below.

Part I—Synthesis of (Z)—N-(((3-(3-(Benzyloxy)phenyl)-1H-pyrazol-5-yl)amino)(tert-butylamino)methylene)-4-(trifluoromethyl)benzamide

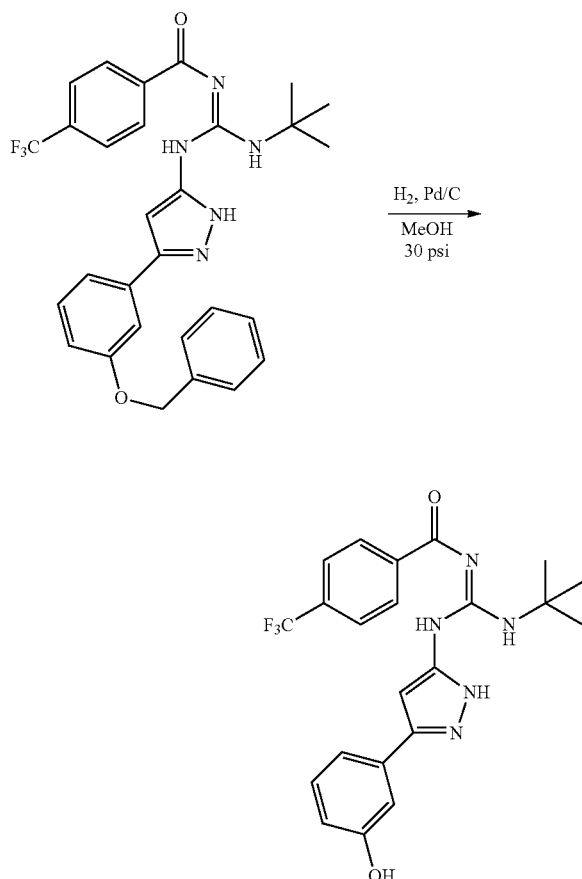




## 317

The title compound was prepared from 4-(trifluoromethyl) benzoyl chloride, 2-methylpropan-2-amine, and 3-(3-(benzyloxy)phenyl)-1H-pyrazol-5-amine based on synthetic procedures described in Example 4.

Part II—Synthesis of (Z)—N-((tert-Butylamino)((3-(3-hydroxyphenyl)-1H-pyrazol-5-yl)amino)methylene)-4-(trifluoromethyl)benzamide (A-564)



(Z)—N-(((3-(3-(Benzyloxy)phenyl)-1H-pyrazol-5-yl)amino)(tert-butylamino)methylene)-4-(trifluoromethyl)benzamide (170 mg) was dissolved in methanol (10 mL) and the solution was degassed with nitrogen. To the solution was added 10% palladium on carbon (34 mg, 0.1 equiv). The mixture was then subjected to hydrogen gas at 30 psi pressure in a Parr shaker. The reaction was checked periodically for completion. Upon completion, the reaction mixture was filtered through celite, and the filtrate was concentrated in vacuo to provide the crude product, which was purified by silica chromatography (9:1 to 55:45 hexanes:EtOAc) to provide the title compound (77 mg, 54% yield). <sup>1</sup>HNMR (400 MHz, DMSO-d<sub>6</sub>) δ 13.18 (s, 1H), 12.79 (s, 1H), 9.63 (s, 1H), 9.02 (s, 1H), 8.28 (d, 2H), 7.82 (d, 2H), 7.23 (m, 1H), 7.18 (m, 1H), 7.09 (m, 1H), 6.79 (m, 1H), 6.49 (s, 1H), 3.98 (m, 1H), 1.95 (s, 1H), 1.56 (s, 9H), 1.12 (m, 1H), 0.82 (m, 1H); MS (EI+) m/z: 445.94, 467.97; HPLC (Method B): 6.08 min.

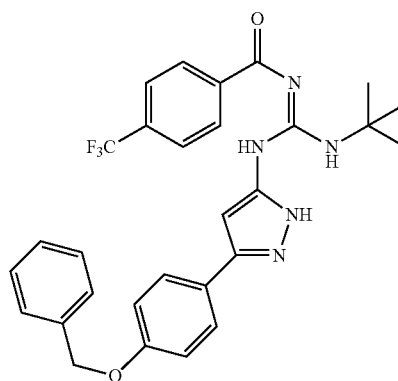
## 318

## Example 11

Preparation of (Z)—N-((tert-Butylamino)((3-(4-hydroxyphenyl)-1H-pyrazol-5-yl)amino)methylene)-4-(trifluoromethyl)benzamide

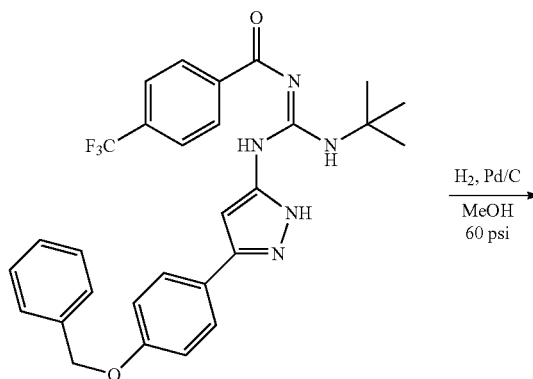
The title compound was prepared according to the procedures described below.

Part I—Synthesis of (Z)—N-(((3-(4-(Benzyloxy)phenyl)-1H-pyrazol-5-yl)amino)(tert-butylamino)methylene)-4-(trifluoromethyl)benzamide



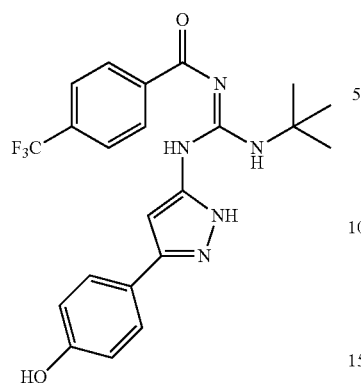
The title compound was prepared from 4-(trifluoromethyl) benzoyl chloride, 2-methylpropan-2-amine, and 3-(4-(benzyloxy)phenyl)-1H-pyrazol-5-amine based on synthetic procedures described in Example 4.

Part II—Synthesis of (Z)—N-((tert-Butylamino)((3-(4-hydroxyphenyl)-1H-pyrazol-5-yl)amino)methylene)-4-(trifluoromethyl)benzamide



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-continued



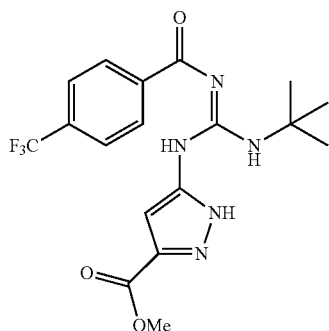
(Z)—N-(((3-(4-(Benzyloxy)phenyl)-1H-pyrazol-5-yl) amino)(tert-butylamino)methylene)-4-(trifluoromethyl)benzamide (150 mg) was dissolved in methanol (10 mL) and the solution was degassed with nitrogen. To the solution was added 10% palladium on carbon (30 mg, 0.1 equiv). The mixture was subjected to hydrogen gas at 60 psi pressure in a Parr shaker. The reaction was checked periodically for completion. Upon completion, the reaction mixture was filtered through celite, and the filtrate was concentrated in vacuo to provide the crude product, which was purified by silica chromatography (9:1 to 55:45 hexanes:EtOAc) to provide the title compound (85 mg, 68% yield).

## Example 12

Preparation of (Z)-5-(3-(tert-Butyl)-2-(4-(trifluoromethyl)benzoyl)guanidino)-1H-pyrazole-3-carboxylic acid (A-565)

The title compound was prepared according to the procedures described below.

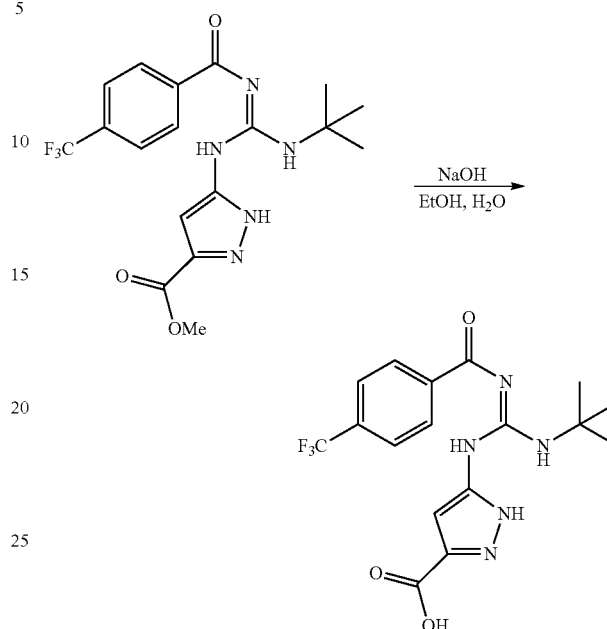
Part I—Synthesis of (Z)-Methyl 5-(3-(tert-butyl)-2-(4-(trifluoromethyl)benzoyl)guanidino)-1H-pyrazole-3-carboxylate



The title compound was prepared from 4-(trifluoromethyl)benzoyl chloride, 2-methylpropan-2-amine, and methyl 5-amino-1H-pyrazole-3-carboxylate based on synthetic procedures described in Example 4.

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Part II—Synthesis of (Z)-5-(3-(tert-Butyl)-2-(4-(trifluoromethyl)benzoyl)guanidino)-1H-pyrazole-3-carboxylic acid (A-565)



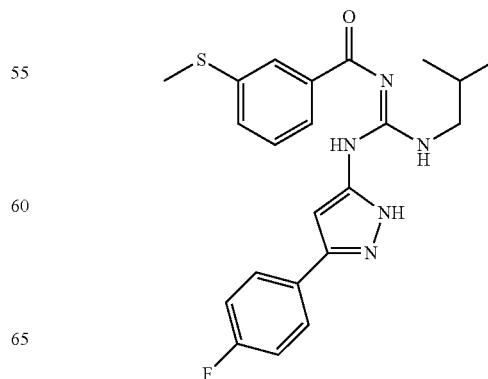
To a solution of (4-methyl 5-(3-(tert-butyl)-2-(4-(trifluoromethyl)benzoyl)guanidino)-1H-pyrazole-3-carboxylate (70 mg) in ethanol (3 mL) was added aqueous 2M NaOH (200  $\mu$ L). The reaction was stirred at room temperature for 2 days. The solvent was removed in vacuo, and the sample was diluted with water. To the mixture was added 1N HCl (400  $\mu$ L, aqueous). The resulting solid was collected by filtration, washed with water, and concentrated in vacuo to provide the title compound (32 mg, 68% yield).  $^1\text{H}$ NMR (400 MHz, DMSO- $d_6$ )  $\delta$  13.62 (bs, 1H), 12.65 (s, 1H), 8.80 (s, 1H), 8.25 (d, 2H), 7.81 (d, 2H), 6.58 (s, 1H), 1.54 (s, 9H); MS (EI+)  $m/z$ : 396.17 (M-1); HPLC (Method B): 5.48 min.

## Example 13

Preparation of (Z)—N-(((3-(4-Fluorophenyl)-1H-pyrazol-5-yl)amino)(isobutylamino)methylene)-3-(methylsulfinyl)benzamide (A-566)

The title compound was prepared according to the procedures described below.

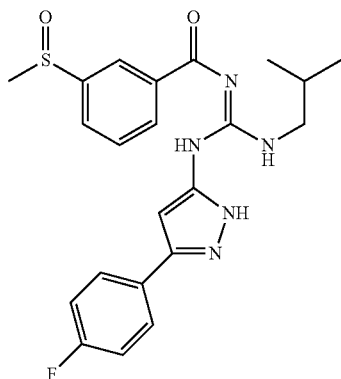
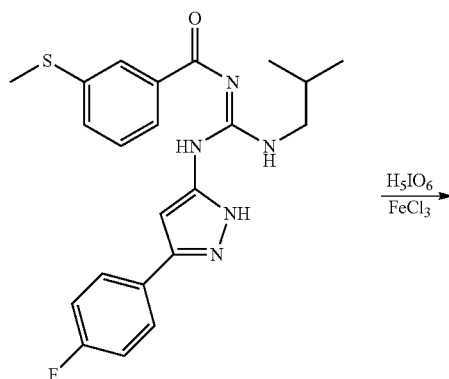
Part I—Synthesis of (Z)—N-[[[3-(4-Fluorophenyl)-1H-pyrazol-5-yl]amino]-(isobutylamino)methylene]-3-methylsulfinyl-benzamide



## 321

The title compound was prepared from 3-(methylthio)benzoyl chloride, 2-methylpropan-1-amine, and 3-(4-fluorophenyl)-1H-pyrazol-5-amine based on synthetic procedures described in Example 4.

Part II—Synthesis of (Z)—N-(((3-(4-Fluorophenyl)-1H-pyrazol-5-yl)amino)(isobutylamino) methylene)-3-(methylsulfinyl)benzamide (A-566)



To an orange solution of (Z)—N-[[[3-(4-fluorophenyl)-1H-pyrazol-5-yl]amino]-(isobutylamino)methylene]-3-methylsulfanyl-benzamide (500 mg, 1.175 mmol) and ferric chloride trihydrate (9.5 mg, 0.035 mmol) in acetone:acetonitrile (1:1) was added periodic acid (295 mg, 1.3 mmol) in one portion. After stirring the resulting mixture at room temperature for ca. 21 hr, the reaction was quenched by adding aqueous sodium thiosulfate. The product was extracted with DCM, and the organic layer was washed with brine and dried over  $\text{MgSO}_4$ . The drying reagent was removed by filtration, and the filtrate was concentrated onto silica gel and purified by silica chromatography (50-90% EtOAc in hexanes) to provide the title compound (77% yield). MS (EI+) m/z: 442.17.

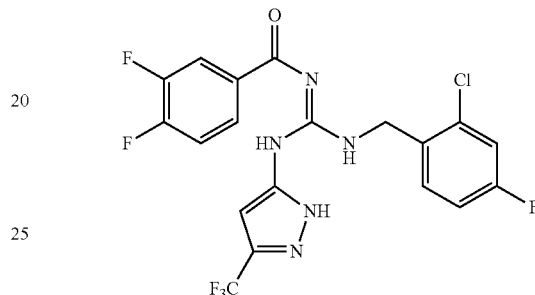
## 322

## Example 14

Preparation of (E)-N-(3-(2-chloro-4-fluorobenzyl)-4-oxo-7-(trifluoromethyl)-3,4-dihydropyrazolo[1,5-a][1,3,5]triazin-2(1H)-ylidene)-3,4-difluorobenzamide (A-567)

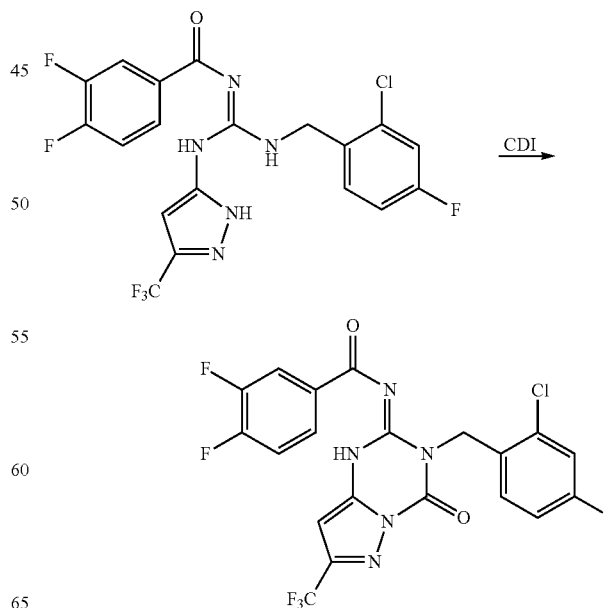
The title compound was prepared according to the procedures described below.

Part I—Synthesis of (Z)—N-(((2-chloro-4-fluorobenzyl)amino)((3-(trifluoromethyl)-1H-pyrazol-5-yl)amino)methylene)-3,4-difluorobenzamide



The title compound was prepared from 3,4-difluorobenzoyl chloride; (2-chloro-4-fluorophenyl)methanamine; and 3-(trifluoromethyl)-1H-pyrazol-5-amine based on synthetic procedures described in Example 4.

Part II—Synthesis of (E)-N-(3-(2-chloro-4-fluorobenzyl)-4-oxo-7-(trifluoromethyl)-3,4-dihydropyrazolo[1,5-a][1,3,5]triazin-2(1H)-ylidene)-3,4-difluorobenzamide (A-567)



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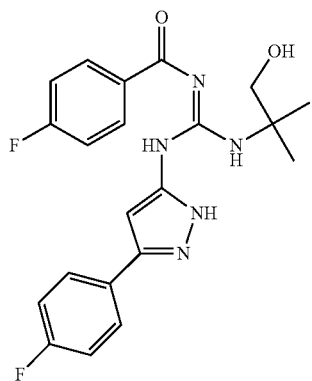
To a solution of (Z)-N-(((2-chloro-4-fluorobenzyl)amino)((3-(trifluoromethyl)-1H-pyrazol-5-yl)amino)methylene)-3,4-difluorobenzamide (50 mg, 0.11 mmol) in THF (1 mL) was added 1,1'-carbonyldiimidazole (CDI) (26 mg, 0.16 mmol). The reaction mixture was stirred at room temperature for 30 minutes. Purification by silica chromatography (EtOAc:hexanes) provided the title compound (14 mg, 27% yield). HPLC (Method A): 11.1 min.

## Example 15

Preparation of (Z)-4-fluoro-N-(8-(4-fluorophenyl)-4,4-dimethyl-4,5-dihydro-1H-pyrazolo[1,5-a][1,3,5]triazepin-2(3H)-ylidene)benzamide (A-568)

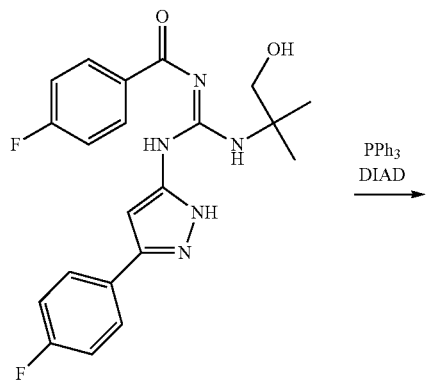
The title compound was prepared according to the procedures described below.

Part I—Synthesis of (Z)-4-fluoro-N-(((3-(4-fluorophenyl)-1H-pyrazol-5-yl)amino)((1-hydroxy-2-methylpropan-2-yl)amino)methylene)benzamide



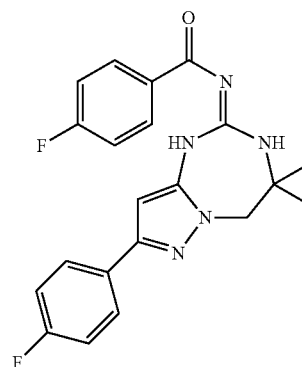
The title compound was prepared based on synthetic procedures described in Example 4.

Part II—Synthesis of (Z)-4-fluoro-N-(8-(4-fluorophenyl)-4,4-dimethyl-4,5-dihydro-1H-pyrazolo[1,5-a][1,3,5]triazepin-2(3H)-ylidene)benzamide (A-568)



## 324

-continued



To a solution of (Z)-4-fluoro-N-(((3-(4-fluorophenyl)-1H-pyrazol-5-yl)amino)((1-hydroxy-2-methylpropan-2-yl)amino)methylene)benzamide (25 mg, 0.06 mmol) in anhydrous THF (0.5 mL) under a nitrogen atmosphere was added triphenylphosphine (19 mg, 0.07 mmol) followed by diisopropyl azodicarboxylate (DIAD) (14  $\mu$ L, 0.07 mmol). The reaction mixture was stirred at room temperature for 30 minutes and purification by silica chromatography (EtOAc:hexanes) afforded the title compound (21 mg, 88% yield). LCMS (ESI). found (M-H)<sup>-</sup>, 394.15; <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>)  $\delta$  12.91 (s, 1H), 9.35 (s, 1H), 8.18 (m, 2H), 7.75 (m, 2H), 7.31 (m, 4H), 7.17 (s, 1H), 3.75 (s, 2H), 1.39 (s, 6H).

## Example 16

Preparation of (S,E)-4-fluoro-N-(2-(4-fluorophenyl)-8,9,9a,10-tetrahydro-4H-pyrazolo[1,5-a]pyrrolo[1,2-e][1,3,5]triazepin-5(7H)-ylidene)benzamide (A-569)

The title compound was prepared according to the procedures described below.

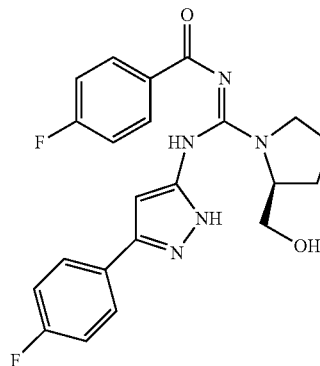
Part I—Synthesis of (S,E)-4-fluoro-N-(((3-(4-fluorophenyl)-1H-pyrazol-5-yl)amino)((2-(hydroxymethyl)pyrrolidin-1-yl)methylene)benzamide

50

55

60

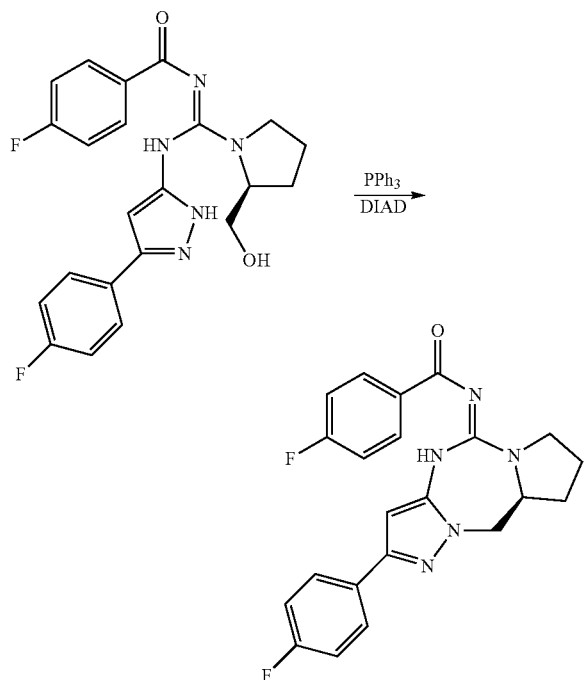
65



## 325

The title compound was prepared based on synthetic procedures described in Example 4.

Part II—Synthesis of (S,E)-4-fluoro-N-(2-(4-fluorophenyl)-8,9,9a,10-tetrahydro-4H-pyrazolo[1,5-a]pyrrolo[1,2-e][1,3,5]triazepin-5(7H)-ylidene)benzamide (A-569)



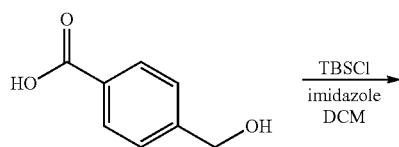
To a solution of (S,E)-4-fluoro-N-(((3-(4-fluorophenyl)-1H-pyrazol-5-yl)amino)(2-(hydroxymethyl)pyrrolidin-1-yl)methylene)benzamide (30 mg, 0.07 mmol) in anhydrous THF (0.4 mL) under a nitrogen atmosphere was added triphenylphosphine (22 mg, 0.085 mmol) followed by DIAD (16  $\mu$ L, 0.085 mmol). The reaction mixture was stirred at room temperature for 30 minutes and purification by silica chromatography (EtOAc:hexanes) provided the title compound (22 mg, 77% yield). LCMS (ESI). found (M-H), 406.06. HPLC (Method A): 7.11 min.

## Example 17

Preparation of (Z)-3,4-Difluoro-N-(((3-(4-(hydroxymethyl)phenyl)-1H-pyrazol-5-yl)amino)(isobutylamino)methylene)benzamide (A-570)

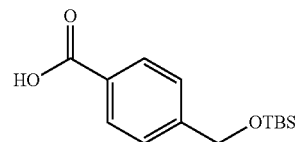
The title compound was prepared according to the procedures described below.

Part I—Synthesis of 4-(((tert-Butyldimethylsilyl)oxy)methyl)benzoic acid



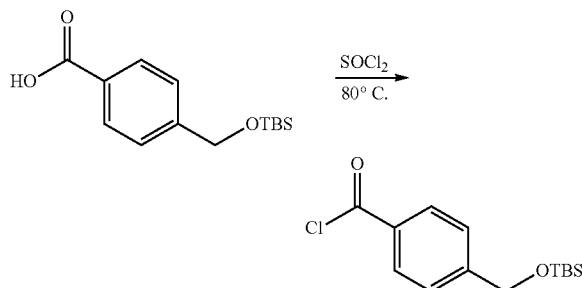
## 326

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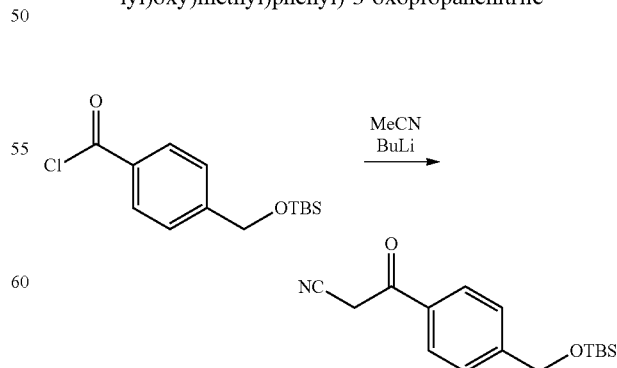
To a solution of 4-hydroxymethylbenzoic acid (1 g) in DCM (66 mL) was added imidazole (985 mg, 2.2 equiv) followed by the addition of t-butyldimethylsilyl chloride (TBSCl) (1.09 g, 1.1 equiv). The reaction mixture was stirred at room temperature for 3 days and was diluted with DCM (50 mL) and 1 N HCl. The aqueous phase was extracted with DCM, and the combined organic extracts were dried over sodium sulfate and concentrated in vacuo to provide the title compound (1.44 g, 82% yield).

Part II—Synthesis of 4-(((tert-Butyldimethylsilyl)oxy)methyl)benzoyl chloride



4-[[t-Butyl(dimethyl)silyl]oxymethyl]benzoic acid (1.44 g) was suspended in thionyl chloride and the mixture was heated to 80° C. for 45 minutes. The resulting solution was concentrated in vacuo. Residual thionyl chloride and HCl were removed by subsequent concentration from toluene (twice). The crude residue was carried on to the next reaction step without purification.

Part III—Synthesis of 3-(4-(((tert-Butyldimethylsilyl)oxy)methyl)phenyl)-3-oxopropanenitrile

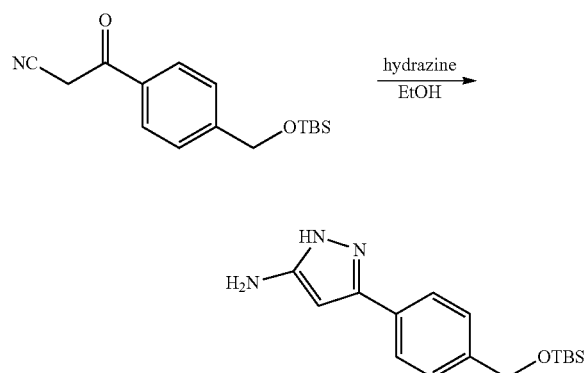


To a chilled (−78° C.) solution of acetonitrile (MeCN) (1.13 mL, 4 equiv) in THF (54 mL) was added butyllithium

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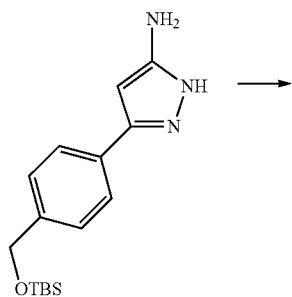
(BuLi) (1.62 mL, 10 M in hexanes, 3 equiv) dropwise, keeping the temperature under  $-60^{\circ}\text{C}$ . The mixture was stirred for 15 minutes at  $-78^{\circ}\text{C}$ . A solution of 4-(((tert-butyldimethylsilyl)oxy)methyl)benzoyl chloride (1.44 g) in THF (5 mL) was slowly added, and the reaction mixture was stirred at  $-78^{\circ}\text{C}$  for 45 minutes. The reaction was then quenched with aqueous ammonium chloride and diluted with EtOAc. The phases were separated and the organic phase was washed with brine, dried over sodium sulfate, and concentrated onto silica gel. Purification by silica chromatography (9:1 hexanes:EtOAc to EtOAc) provided the title compound (370 mg, 24% yield) and the de-silylated product (330 mg).

Part IV—Synthesis of 3-(4-(((tert-Butyldimethylsilyl)oxy)methyl)phenyl)-1H-pyrazol-5-amine



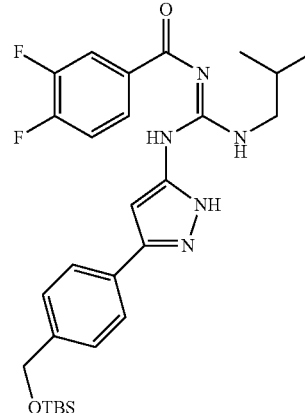
4-[[t-Butyldimethylsilyloxy]benzoyl acetonitrile (370 mg) and hydrazine (0.044 mL, 1.1 equiv) were dissolved in ethanol (13 mL), and the reaction was heated at reflux overnight. The solution was concentrated in vacuo and the resulting residue was purified by silica chromatography (3:1 hexanes:EtOAc to EtOAc) to provide the title compound (160 mg, 41% yield).

Part V—Synthesis of (Z)—N-(((3-(4-(((tert-Butyldimethylsilyl)oxy)methyl)phenyl)-1H-pyrazol-5-yl)amino)(isobutylamino)methylene)-3,4-difluorobenzamide



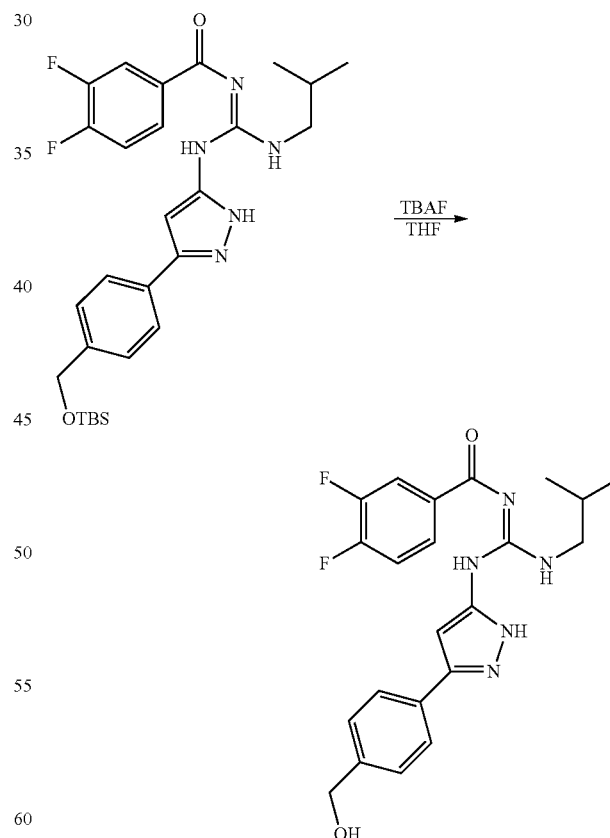
## 328

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The title compound was prepared from 3,4-difluorobenzoyl chloride; 2-methylpropan-1-amine; and 3-(4-(((tert-butyldimethylsilyloxy)methyl)phenyl)-1H-pyrazol-5-amine based on synthetic procedures described in Example 4.

Part VI—Synthesis of (Z)-3,4-Difluoro-N-(((3-(4-(hydroxymethyl)phenyl)-1H-pyrazol-5-yl)amino)(isobutylamino)methylene)benzamide (A-570)



To a solution of (Z)—N-(((3-(4-(((tert-butyldimethylsilyl)oxy)methyl)phenyl)-1H-pyrazol-5-yl)amino)(isobutylamino)methylene)-3,4-difluorobenzamide (60 mg) in THF (2 mL) was added tetrabutylammonium fluoride (TBAF) (1 M in THF, 0.122 mL, 1.1 equiv). The solution was stirred at

## 329

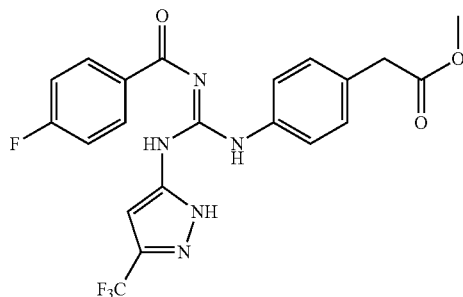
room temperature for one hour, and partitioned between water and EtOAc. The organic phase was dried over sodium sulfate, concentrated onto silica gel, and purified by silica chromatography to provide the title compound (23 mg, 49% yield). <sup>1</sup>HNMR (400 MHz, DMSO-d<sub>6</sub>) δ 13.18 (s, 1H), 12.60 (s, 1H), 8.96 (t, 1H), 8.00 (m, 2H), 7.70 (d, 2H), 7.48 (m, 1H), 7.40 (d, 2H), 6.60 (s, 1H), 5.23 (t, 1H), 4.50 (d, 2H), 3.43 (m, 2H), 1.92 (m, 1H), 1.00 (d, 6H); MS (EI+) m/z: 428.07; HPLC (Method B): 4.67 min.

## Example 18

Preparation of (Z)-2-(4-(2-(4-Fluorobenzoyl)-3-(3-(trifluoromethyl)-1H-pyrazol-5-yl)guanidino)phenyl)acetic acid

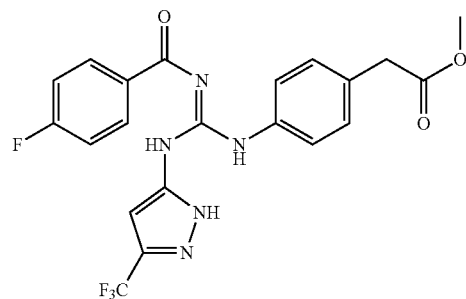
The title compound was prepared according to the procedures described below.

Part I—Synthesis of (Z)-Methyl 2-(4-(2-(4-fluorobenzoyl)-3-(3-(trifluoromethyl)-1H-pyrazol-5-yl)guanidino)phenyl)acetate

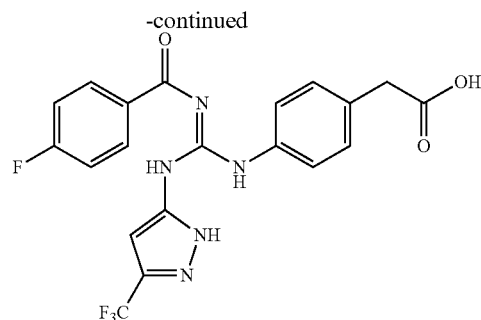


The title compound was prepared from 4-fluorobenzoyl chloride, methyl 2-(4-aminophenyl)acetate, and 3-(trifluoromethyl)-1H-pyrazol-5-amine based on synthetic procedures described in Example 4.

Part II—Synthesis of (Z)-2-(4-(2-(4-Fluorobenzoyl)-3-(3-(trifluoromethyl)-1H-pyrazol-5-yl)guanidino)phenyl)acetic acid



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To a solution of (4-methyl 2-(4-(2-(4-fluorobenzoyl)-3-(3-(trifluoromethyl)-1H-pyrazol-5-yl)guanidino)phenyl)acetate (400 mg) in methanol (20 mL) was added aqueous 6N NaOH (0.5 mL). The solution was held at room temperature overnight, concentrated in vacuo, and dissolved in water. The solution was acidified with 6 N HCl until precipitation appeared to be complete. The resulting precipitate was collected by filtration and dried in a vacuum oven. The crude product was purified by silica chromatography (99:1 DCM: AcOH to 84:15:1 DCM:MeOH:AcOH) to provide the title compound (5 mg, 1% yield).

## Example 19

Exemplary compounds described in above Examples were tested for activity against F<sub>1</sub>F<sub>0</sub>-ATPase by measuring the ability of the compounds to inhibit ATP synthesis. In addition, the compounds were assessed for cytotoxicity in Ramos cells. Results of the biological activity tests are shown in Table 4 below. Inhibition of F<sub>1</sub>F<sub>0</sub>-ATPase activity in synthesizing ATP and cytotoxicity in Ramos cells were measured according to the procedures described in K. M. Johnson et al. *Chemistry & Biology* 2005, 12, 485-496. The symbol “NA” indicates that data was not available.

TABLE 4

Compound No.	ATP Syn IC <sub>50</sub> (μM)	Ramos Cell EC <sub>50</sub> (μM)
A-1	<10	<10
A-2	<10	<10
A-3	<10	<10
A-4	<10	<10
A-5	<10	<10
A-6	<10	<10
A-7	<10	<10
A-8	<10	<10
A-9	<10	<10
A-10	<10	<10
A-11	<10	<10
A-12	<10	<10
A-13	<10	<10
A-14	<10	<10
A-15	<10	<10
A-16	<10	<10
A-17	<10	<10
A-18	<10	<10
A-19	<10	<10
A-20	<10	<10
A-21	<10	<10
A-22	<10	<10
A-23	<10	<10
A-24	<10	<10
A-25	<10	<10
A-26	<10	<10
A-27	<10	<10
A-28	<10	<10
A-29	<10	<10

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TABLE 4-continued

Compound No.	ATP Syn IC <sub>50</sub> (μM)	Ramos Cell EC <sub>50</sub> (μM)
A-30	<10	<10
A-31	<10	<10
A-32	<10	<10
A-33	<10	<10
A-34	<10	<10
A-35	<10	<10
A-36	<10	<10
A-37	<10	>10
A-38	<10	<10
A-39	<10	NA
A-40	<10	<10
A-41	<10	<10
A-42	<10	<10
A-43	<10	<10
A-44	>10	>10
A-45	<10	>10
A-46	<10	<10
A-47	<10	<10
A-48	<10	<10
A-49	<10	<10
A-50	<10	<10
A-51	<10	<10
A-52	<10	<10
A-53	<10	<10
A-54	<10	<10
A-55	<10	>10
A-56	<10	>10
A-57	<10	<10
A-58	<10	>10
A-59	<10	>10
A-60	<10	<10
A-61	<10	>10
A-62	<10	<10
A-63	<10	>10
A-64	<10	<10
A-65	<10	<10
A-66	<10	<10
A-67	<10	<10
A-68	<10	<10
A-69	<10	<10
A-70	<10	<10
A-71	<10	<10
A-72	<10	<10
A-73	<10	<10
A-74	<10	<10
A-75	<10	<10
A-76	<10	<10
A-77	<10	<10
A-78	<10	<10
A-79	<10	<10
A-80	<10	<10
A-81	<10	<10
A-82	<10	<10
A-83	<10	<10
A-84	<10	>10
A-85	<10	>10
A-86	<10	>10
A-87	<10	<10
A-88	<10	<10
A-89	<10	<10
A-90	<10	<10
A-91	<10	<10
A-92	<10	<10
A-93	<10	<10
A-94	<10	<10
A-95	<10	<10
A-96	<10	<10
A-97	<10	<10
A-98	<10	<10
A-99	<10	<10
A-100	<10	<10
A-101	<10	<10
A-102	<10	<10
A-103	<10	<10
A-104	<10	>10
A-105	<10	<10
A-106	<10	<10

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TABLE 4-continued

Compound No.	ATP Syn IC <sub>50</sub> (μM)	Ramos Cell EC <sub>50</sub> (μM)
A-107	<10	<10
A-108	<10	<10
A-109	<10	<10
A-110	<10	<10
A-111	<10	<10
A-112	<10	>10
A-113	<10	<10
A-114	<10	<10
A-115	<10	<10
A-116	<10	<10
A-117	<10	<10
A-118	<10	<10
A-119	<10	<10
A-120	<10	<10
A-121	<10	>10
A-122	<10	<10
A-123	<10	<10
A-124	<10	>10
A-125	<10	<10
A-126	>10	>10
A-127	<10	>10
A-128	<10	<10
A-129	<10	<10
A-130	<10	<10
A-131	<10	<10
A-132	<10	<10
A-133	<10	<10
A-134	<10	<10
A-135	<10	<10
A-136	<10	<10
A-137	<10	<10
A-138	<10	<10
A-139	>10	>10
A-140	>10	>10
A-141	<10	<10
A-142	<10	<10
A-143	<10	<10
A-144	<10	<10
A-145	<10	<10
A-146	<10	<10
A-147	<10	<10
A-148	>10	>10
A-149	<10	<10
A-150	<10	<10
A-151	<10	>10
A-152	<10	<10
A-153	<10	<10
A-154	<10	<10
A-155	<10	<10
A-156	>10	>10
A-157	>10	>10
A-158	>10	>10
A-159	<10	<10
A-160	<10	>10
A-161	>10	>10
A-162	<10	<10
A-163	<10	<10
A-164	<10	<10
A-165	>10	>10
A-166	<10	<10
A-167	<10	<10
A-168	<10	<10
A-169	<10	<10
A-170	<10	<10
A-171	<10	<10
A-172	<10	<10
A-173	<10	<10
A-174	<10	<10
A-175	<10	>10
A-176	<10	<10
A-177	<10	<10
A-178	<10	<10
A-179	>10	>10
A-180	<10	>10
A-181	<10	<10
A-182	<10	<10
A-183	<10	<10



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TABLE 4-continued

Compound No.	ATP Syn IC <sub>50</sub> (μM)	Ramos Cell EC <sub>50</sub> (μM)
A-184	>10	>10
A-185	<10	<10
A-186	>10	>10
A-187	<10	<10
A-188	<10	>10
A-189	<10	<10
A-190	>10	>10
A-191	>10	>10
A-192	<10	<10
A-193	<10	>10
A-194	NA	>10
A-195	<10	<10
A-196	<10	<10
A-197	<10	<10
A-198	<10	<10
A-199	<10	>10
A-200	<10	>10
A-201	<10	>10
A-202	<10	>10
A-203	<10	<10
A-204	<10	<10
A-205	<10	<10
A-206	<10	<10
A-207	>10	>10
A-208	>10	>10
A-209	<10	<10
A-210	<10	<10
A-211	<10	>10
A-212	<10	<10
A-213	<10	<10
A-214	<10	<10
A-215	>10	>10
A-216	<10	<10
A-217	<10	<10
A-218	<10	<10
A-219	<10	<10
A-220	<10	<10
A-221	<10	<10
A-222	<10	<10
A-223	<10	<10
A-224	<10	>10
A-225	<10	<10
A-226	<10	<10
A-227	<10	>10
A-228	<10	>10
A-229	<10	<10
A-230	<10	<10
A-231	<10	<10
A-232	<10	<10
A-233	<10	<10
A-234	<10	<10
A-235	<10	<10
A-236	<10	<10
A-237	<10	<10
A-238	<10	<10
A-239	<10	>10
A-240	<10	<10
A-241	<10	<10
A-242	<10	<10
A-243	<10	<10
A-244	<10	<10
A-245	<10	<10
A-246	<10	<10
A-247	<10	<10
A-248	<10	<10
A-249	<10	<10
A-250	<10	<10
A-251	<10	<10
A-252	<10	<10
A-253	<10	<10
A-254	<10	<10
A-255	<10	<10
A-256	<10	<10
A-257	<10	<10
A-258	<10	<10
A-259	<10	<10
A-260	<10	<10

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TABLE 4-continued

Compound No.	ATP Syn IC <sub>50</sub> (μM)	Ramos Cell EC <sub>50</sub> (μM)
A-261	<10	<10
A-262	<10	<10
A-263	<10	<10
A-264	<10	<10
A-265	<10	<10
A-266	<10	<10
A-267	<10	<10
A-268	<10	<10
A-269	<10	<10
A-270	<10	>10
A-271	<10	<10
A-272	<10	<10
A-273	<10	<10
A-274	<10	<10
A-275	<10	<10
A-276	<10	<10
A-277	<10	>10
A-278	<10	>10
A-279	<10	<10
A-280	<10	>10
A-281	<10	<10
A-282	<10	<10
A-283	<10	<10
A-284	<10	<10
A-285	<10	<10
A-286	<10	<10
A-287	<10	<10
A-288	<10	<10
A-289	<10	<10
A-290	<10	<10
A-291	<10	<10
A-292	<10	<10
A-293	<10	<10
A-294	<10	>10
A-295	<10	<10
A-296	<10	<10
A-297	<10	<10
A-298	<10	<10
A-299	<10	<10
A-300	<10	<10
A-301	<10	<10
A-302	<10	<10
A-303	<10	<10
A-304	<10	<10
A-305	<10	<10
A-306	<10	<10
A-307	<10	<10
A-308	<10	<10
A-309	<10	<10
A-310	<10	<10
A-311	<10	<10
A-312	<10	<10
A-313	<10	<10
A-314	<10	<10
A-315	<10	>10
A-316	<10	<10
A-317	<10	<10
A-318	>10	<10
A-319	<10	<10
A-320	<10	<10
A-321	<10	<10
A-322	<10	<10
A-323	<10	<10
A-324	<10	<10
A-325	<10	<10
A-326	<10	>10
A-327	>10	>10
A-328	<10	<10
A-329	<10	<10
A-330	>10	>10
A-331	<10	<10
A-332	<10	>10
A-333	<10	>10
A-334	<10	<10
A-335	<10	<10
A-336	<10	<10
A-337	>10	>10

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TABLE 4-continued

Compound No.	ATP Syn IC <sub>50</sub> (μM)	Ramos Cell EC <sub>50</sub> (μM)
A-338	<10	<10
A-339	10	>10
A-340	<10	<10
A-341	<10	<10
A-342	<10	<10
A-343	<10	>10
A-344	<10	<10
A-345	>10	>10
A-346	<10	<10
A-347	<10	<10
A-348	<10	<10
A-349	<10	<10
A-350	<10	<10
A-351	<10	<10
A-352	<10	<10
A-354	NA	<10
A-355	NA	>10
A-356	NA	<10
A-357	NA	>10
A-358	NA	<10
A-359	<10	<10
A-360	<10	<10
A-361	<10	<10
A-362	<10	<10
A-363	<10	<10
A-364	<10	<10
A-365	<10	<10
A-366	<10	<10
A-367	<10	<10
A-368	<10	<10
A-369	<10	<10
A-370	<10	<10
A-371	>10	>10
A-372	<10	>10
A-373	<10	<10
A-374	<10	<10
A-375	<10	<10
A-376	<10	<10
A-377	<10	<10
A-378	<10	<10
A-379	<10	<10
A-380	<10	<10
A-381	<10	<10
A-382	<10	<10
A-383	<10	<10
A-384	<10	<10
A-385	<10	<10
A-386	<10	<10
A-387	<10	>10
A-388	<10	<10
A-389	<10	<10
A-390	<10	>10
A-391	>10	>10
A-392	<10	<10
A-393	<10	<10
A-394	<10	<10
A-395	<10	<10
A-396	<10	<10
A-397	<10	<10
A-398	<10	<10
A-399	<10	<10
A-400	<10	<10
A-401	<10	<10
A-402	<10	<10
A-403	<10	<10
A-404	<10	>10
A-405	<10	<10
A-406	<10	>10
A-407	<10	>10
A-408	<10	<10
A-409	<10	>10
A-410	<10	>10
A-411	<10	>10
A-412	<10	>10
A-413	<10	>10
A-414	<10	<10
A-415	<10	>10

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TABLE 4-continued

Compound No.	ATP Syn IC <sub>50</sub> (μM)	Ramos Cell EC <sub>50</sub> (μM)
A-416	<10	>10
A-417	<10	<10
A-418	<10	<10
A-419	<10	<10
A-420	<10	<10
A-421	<10	<10
A-422	<10	<10
A-423	<10	<10
A-424	<10	<10
A-425	<10	<10
A-426	<10	>10
A-427	<10	<10
A-428	<10	>10
A-429	<10	<10
A-430	<10	<10
A-431	<10	<10
A-432	<10	>10
A-433	<10	<10
A-434	<10	>10
A-435	<10	<10
A-436	<10	>10
A-437	<10	<10
A-438	<10	<10
A-439	<10	<10
A-440	<10	<10
A-441	<10	<10
A-442	<10	<10
A-443	<10	<10
A-444	<10	>10
A-445	<10	<10
A-446	<10	>10
A-447	<10	>10
A-448	<10	<10
A-449	<10	<10
A-450	<10	<10
A-451	<10	<10
A-452	<10	<10
A-453	<10	<10
A-454	<10	<10
A-455	<10	<10
A-456	<10	<10
A-457	<10	<10
A-458	<10	<10
A-459	<10	<10
A-460	<10	<10
A-461	<10	<10
A-462	>10	>10
A-463	<10	>10
A-464	>10	>10
A-465	>10	>10
A-466	>10	>10
A-467	<10	<10
A-468	<10	<10
A-469	<10	<10
A-470	<10	>10
A-471	<10	>10
A-472	<10	>10
A-473	<10	>10
A-474	<10	>10
A-475	<10	>10
A-476	<10	>10
A-477	<10	>10
A-478	<10	<10
A-479	<10	<10
A-480	<10	>10
A-481	<10	>10
A-482	<10	<10
A-483	<10	>10
A-484	<10	<10
A-485	>10	>10
A-486	<10	<10
A-487	<10	<10
A-488	<10	<10
A-489	<10	<10
A-490	<10	<10
A-491	<10	>10
A-492	<10	<10

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TABLE 4-continued

Compound No.	ATP Syn IC <sub>50</sub> (μM)	Ramos Cell EC <sub>50</sub> (μM)
A-493	<10	<10
A-494	<10	<10
A-495	<10	<10
A-496	<10	<10
A-497	<10	<10
A-498	<10	<10
A-499	<10	<10
A-500	<10	<10
A-501	<10	<10
A-502	<10	<10
A-504	<10	NA
A-505	<10	<10
A-506	<10	<10
A-507	NA	<10
A-508	NA	<10
A-509	<10	<10
A-510	<10	<10
A-511	<10	<10
A-512	<10	<10
A-513	<10	<10
A-514	<10	<10
A-515	<10	<10
A-516	<10	<10
A-517	<10	<10
A-518	<10	<10
A-519	<10	<10
A-520	<10	<10
A-521	<10	<10
A-522	<10	<10
A-523	<10	>10
A-524	<10	<10
A-525	<10	<10
A-526	<10	>10
A-527	<10	<10
A-528	<10	>10
A-529	<10	>10
A-530	>10	>10
A-531	<10	>10
A-532	<10	>10
A-533	<10	<10
A-534	<10	<10
A-535	<10	<10
A-536	<10	<10
A-537	<10	<10
A-538	<10	>10
A-539	<10	<10
A-540	<10	<10
A-541	<10	<10
A-542	<10	<10
A-543	<10	<10
A-544	<10	<10
A-545	<10	<10
A-546	<10	<10
A-547	<10	<10
A-548	<10	<10
A-549	<10	<10
A-550	<10	<10
A-551	<10	<10
A-552	<10	<10
A-553	<10	<10
A-554	<10	<10
A-555	<10	<10
A-556	<10	<10
A-557	>10	>10
A-558	<10	<10
A-559	>10	>10
A-560	<10	>10
A-561	<10	<10
A-562	>10	>10
A-563	<10	<10
A-564	<10	<10
A-565	>10	>10
A-566	<10	<10
A-567	<10	<10
A-568	<10	<10
A-569	>10	>10
A-570	>10	>10

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TABLE 4-continued

Compound No.	ATP Syn IC <sub>50</sub> (μM)	Ramos Cell EC <sub>50</sub> (μM)
A-571	<10	<10
A-572	<10	>10
A-573	<10	>10
A-574	<10	>10
A-575	<10	<10
A-576	<10	<10

## INCORPORATION BY REFERENCE

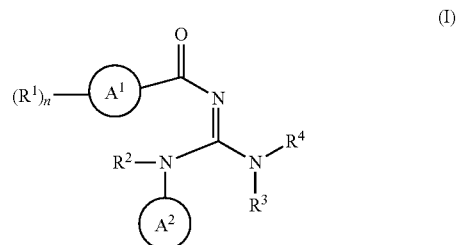
The entire disclosure of each of the patent documents and scientific articles referred to herein is incorporated by reference for all purposes.

## EQUIVALENTS

The invention may be embodied in other specific forms without departing from the spirit or essential characteristics thereof. The foregoing embodiments are therefore to be considered in all respects illustrative rather than limiting the invention described herein. Scope of the invention is thus indicated by the appended claims rather than by the foregoing description, and all changes that come within the meaning and range of equivalency of the claims are intended to be embraced therein.

What is claimed is:

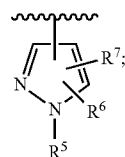
1. A compound represented by Formula I:



including all stereoisomers, geometric isomers, and tautomers; or a pharmaceutically acceptable salt or solvate of any of the foregoing; wherein:

A<sup>1</sup> is phenylene or a six-membered heteroarylene;

A<sup>2</sup> is



R<sup>1</sup> represents independently for each occurrence halogen, haloalkyl, alkyl, cycloalkyl, heterocycloalkyl, hydroxyl, C<sub>1</sub>-C<sub>6</sub>alkoxy, cyano, —CO<sub>2</sub>R<sup>8</sup>, —C(O)R<sup>9</sup>, —S(O)R<sup>9</sup>, —SO<sub>2</sub>R<sup>9</sup>, —SO<sub>2</sub>N(R<sup>10</sup>)(R<sup>11</sup>), —C(O)N(R<sup>10</sup>)(R<sup>11</sup>), —N(R<sup>10</sup>)(R<sup>11</sup>), or —N(R<sup>8</sup>)C(O)R<sup>9</sup>;

R<sup>2</sup> is hydrogen or alkyl;

R<sup>3</sup> is aryl, aralkyl, cycloalkyl, —(C(R<sup>8</sup>)<sub>2</sub>)<sub>m</sub>-cycloalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, —(C(R<sup>8</sup>)<sub>2</sub>)<sub>m</sub>-heterocycloalkyl, alkyl, haloalkyl,

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hydroxyalkyl,  $-(C(R^8)_2)_m$ -alkoxyl,  $-(C(R^8)_2)_m-O-(C(R^8)_2)_m$ -alkoxyl, or  $-(C(R^8)_2)_m-CN$ , wherein said aryl, aralkyl, cycloalkyl, heteroaryl, heteroaralkyl, and heterocycloalkyl are each optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, haloalkyl, hydroxyl, alkyl, cycloalkyl, hydroxyalkyl,  $C_1$ - $C_6$ alkoxy, cyano, and  $-C_1$ - $C_6$ alkylene- $CO_2R^8$ ;

$R^4$  is hydrogen, alkyl, or  $-C(O)R^9$ ; or  $R^3$  and  $R^4$  are taken together with the nitrogen atom to which they are attached to form a 3 to 7 membered heterocyclic ring optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, haloalkyl, hydroxyl, alkyl, cycloalkyl, and  $C_1$ - $C_6$ alkoxy;

$R^5$  is hydrogen or alkyl;

$R^6$  is alkyl, cycloalkyl, haloalkyl, cyano, aryl, aralkyl, heteroaryl, heteroaralkyl,  $-CO_2R^8$ , or  $-C(O)N(R^{10})$  ( $R^{11}$ ), wherein said cycloalkyl, aryl, aralkyl, heteroaryl, and heteroaralkyl are each optionally substituted with 1 or 2 substituents independently selected from the group consisting of halogen, haloalkyl, hydroxyl, alkyl, hydroxyalkyl,  $C_1$ - $C_6$ alkoxy,  $-O$ -aralkyl, and cyano;

$R^7$  is hydrogen, halogen, alkyl, or haloalkyl;

$R^8$  represents independently for each occurrence hydrogen, alkyl, or cycloalkyl; or two occurrences of  $R^8$  attached to the same carbon atom are taken together with said carbon atom to form a saturated carbocyclic ring;

$R^9$  represents independently for each occurrence alkyl or cycloalkyl;

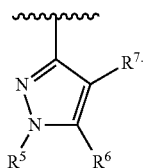
$R^{10}$  and  $R^{11}$  each represent independently for each occurrence hydrogen, alkyl, or cycloalkyl; or  $R^{10}$  and  $R^{11}$  are taken together with the nitrogen atom to which they are attached to form a 3 to 7 membered heterocyclic ring optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, haloalkyl, hydroxyl, alkyl, cycloalkyl, and  $C_1$ - $C_6$ alkoxy;

$n$  is 1, 2, or 3; and

$m$  is 1, 2, 3, 4, or 5.

2. The compound of claim 1, wherein  $A^1$  is phenylene.

3. The compound of claim 1, wherein  $A^2$  is



4. The compound of claim 1, wherein  $R^1$  is halogen or haloalkyl.

5. The compound of claim 1, wherein  $R^1$  is chloro, fluoro, or trifluoromethyl.

6. The compound of claim 1, wherein  $R^2$  and  $R^4$  are hydrogen.

7. The compound of claim 1, wherein  $R^3$  is alkyl or cycloalkyl.

8. The compound of claim 1, wherein  $R^3$  is  $-(C(R^8)_2)_m$ -alkoxyl.

9. The compound of claim 1, wherein  $R^3$  is aryl or aralkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, haloalkyl, alkyl, and cycloalkyl.

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10. The compound of claim 1, wherein  $R^3$  is phenyl optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, haloalkyl, alkyl, and cycloalkyl.

11. The compound of claim 1, wherein  $R^3$  is phenyl substituted with 1 or 2 substituents independently selected from the group consisting of chloro, fluoro, and trifluoromethyl.

12. The compound of claim 1, wherein  $R^3$  is benzyl optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, haloalkyl, alkyl, and cycloalkyl.

13. The compound of claim 1, wherein  $R^5$  is hydrogen.

14. The compound of claim 1, wherein  $R^6$  is alkyl, haloalkyl, cyano, or aryl, wherein said aryl is optionally substituted with 1 or 2 substituents independently selected from the group consisting of halogen, haloalkyl, hydroxyl, and alkyl.

15. The compound of claim 1, wherein  $R^6$  is haloalkyl.

16. The compound of claim 1, wherein  $R^6$  is trifluoromethyl.

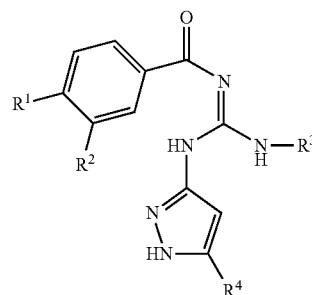
17. The compound of claim 1, wherein  $R^6$  is phenyl optionally substituted with 1 or 2 substituents independently selected from the group consisting of chloro, fluoro, and hydroxyl.

18. The compound of claim 1, wherein  $R^7$  is hydrogen.

19. The compound of claim 1, wherein  $n$  is 1 or 2.

20. A compound represented by Formula I-A1:

(I-A1)



including all stereoisomers, geometric isomers, and tautomers; or a pharmaceutically acceptable salt or solvate of any of the foregoing; wherein:

$R^1$  and  $R^2$  each represent independently for each occurrence hydrogen, chloro, fluoro, or  $-CF_3$ ;

$R^3$  is alkyl, cycloalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, or  $C_1$ - $C_6$ alkylene- $C_1$ - $C_6$ alkoxy, wherein said cycloalkyl, aryl, aralkyl, heteroaryl, and heteroaralkyl are each optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, haloalkyl, hydroxyl, alkyl,  $C_1$ - $C_6$ alkoxy, and cyano; and

$R^4$  is alkyl, cycloalkyl, haloalkyl, cyano, aryl, aralkyl, heteroaryl, or heteroaralkyl, wherein said cycloalkyl, aryl, aralkyl, heteroaryl, and heteroaralkyl are each optionally substituted with 1 or 2 substituents independently selected from the group consisting of halogen, haloalkyl, hydroxyl, alkyl,  $C_1$ - $C_6$ alkoxy, and cyano.

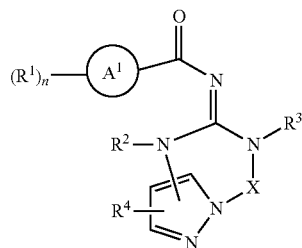
21. The compound of claim 20, wherein  $R^1$  and  $R^2$  are chloro or fluoro.

22. The compound of claim 20, wherein  $R^3$  is phenyl substituted with 1 or 2 substituents independently selected from the group consisting of chloro, fluoro, and trifluoromethyl.

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23. The compound of claim 20, wherein R<sup>4</sup> is trifluoromethyl.

24. A compound represented by Formula II:



including all stereoisomers, geometric isomers, and tautomers; or a pharmaceutically acceptable salt or solvate of any of the foregoing; wherein:

A<sup>1</sup> is phenylene or a six-membered heteroarylene;

X is —[C(R<sup>5</sup>)<sub>2</sub>]<sub>m</sub> or —[C(R<sup>5</sup>)<sub>2</sub>]<sub>p</sub>—C(O)—[C(R<sup>5</sup>)<sub>2</sub>]<sub>p</sub>;

R<sup>1</sup> represents independently for each occurrence halogen, haloalkyl, alkyl, cycloalkyl, heterocycloalkyl, hydroxyl, C<sub>1</sub>-C<sub>6</sub>alkoxy, cyano, —CO<sub>2</sub>R<sup>6</sup>, —C(O)R<sup>7</sup>, —S(O)R<sup>7</sup>, —SO<sub>2</sub>R<sup>7</sup>, —SO<sub>2</sub>N(R<sup>8</sup>)(R<sup>9</sup>), —C(O)N(R<sup>8</sup>)(R<sup>9</sup>), —N(R<sup>8</sup>)(R<sup>9</sup>), or —N(R<sup>6</sup>)C(O)(R<sup>7</sup>);

R<sup>2</sup> is hydrogen or alkyl;

R<sup>3</sup> is hydrogen, aryl, aralkyl, cycloalkyl, —(C(R<sup>6</sup>)<sub>2</sub>)<sub>m</sub>-cycloalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, —(C(R<sup>6</sup>)<sub>2</sub>)<sub>m</sub>-heterocycloalkyl, alkyl, haloalkyl, hydroxyalkyl, —(C(R<sup>6</sup>)<sub>2</sub>)<sub>m</sub>-alkoxyl, —(C(R<sup>6</sup>)<sub>2</sub>)<sub>m</sub>—O—(C(R<sup>6</sup>)<sub>2</sub>)<sub>m</sub>-alkoxyl, or —(C(R<sup>6</sup>)<sub>2</sub>)<sub>m</sub>—CN, wherein said aryl, aralkyl, cycloalkyl, heteroaryl, heteroaralkyl, and heterocycloalkyl are each optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, haloalkyl, hydroxyl, alkyl, cycloalkyl, hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>alkoxy, cyano, and —C<sub>1</sub>-C<sub>6</sub>alkylene-CO<sub>2</sub>R<sup>6</sup>; or R<sup>3</sup> and a single occurrence of R<sup>5</sup> are taken together with the atoms to which they are attached to form a saturated heterocyclic ring;

R<sup>4</sup> is alkyl, cycloalkyl, haloalkyl, cyano, aryl, aralkyl, heteroaryl, heteroaralkyl, —CO<sub>2</sub>R<sup>6</sup>, or —C(O)N(R<sup>8</sup>)(R<sup>9</sup>), wherein said cycloalkyl, aryl, aralkyl, heteroaryl, and heteroaralkyl are each optionally substituted with 1 or 2 substituents independently selected from the group consisting of halogen, haloalkyl, hydroxyl, alkyl, hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>alkoxy, —O-aralkyl, and cyano;

R<sup>5</sup> represents independently for each occurrence hydrogen or alkyl; or R<sup>3</sup> and a single occurrence of R<sup>5</sup> are taken together with the atoms to which they are attached to form a saturated heterocyclic ring;

R<sup>6</sup> represents independently for each occurrence hydrogen, alkyl, or cycloalkyl; or two occurrences of R<sup>6</sup> attached to the same carbon atom are taken together with said carbon atom to form a saturated carbocyclic ring;

R<sup>7</sup> represents independently for each occurrence alkyl or cycloalkyl;

R<sup>8</sup> and R<sup>9</sup> each represent independently for each occurrence hydrogen, alkyl, or cycloalkyl; or R<sup>8</sup> and R<sup>9</sup> are taken together with the nitrogen atom to which they are attached to form a 3 to 7 membered heterocyclic ring optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, haloalkyl, hydroxyl, alkyl, cycloalkyl, and C<sub>1</sub>-C<sub>6</sub>alkoxy;

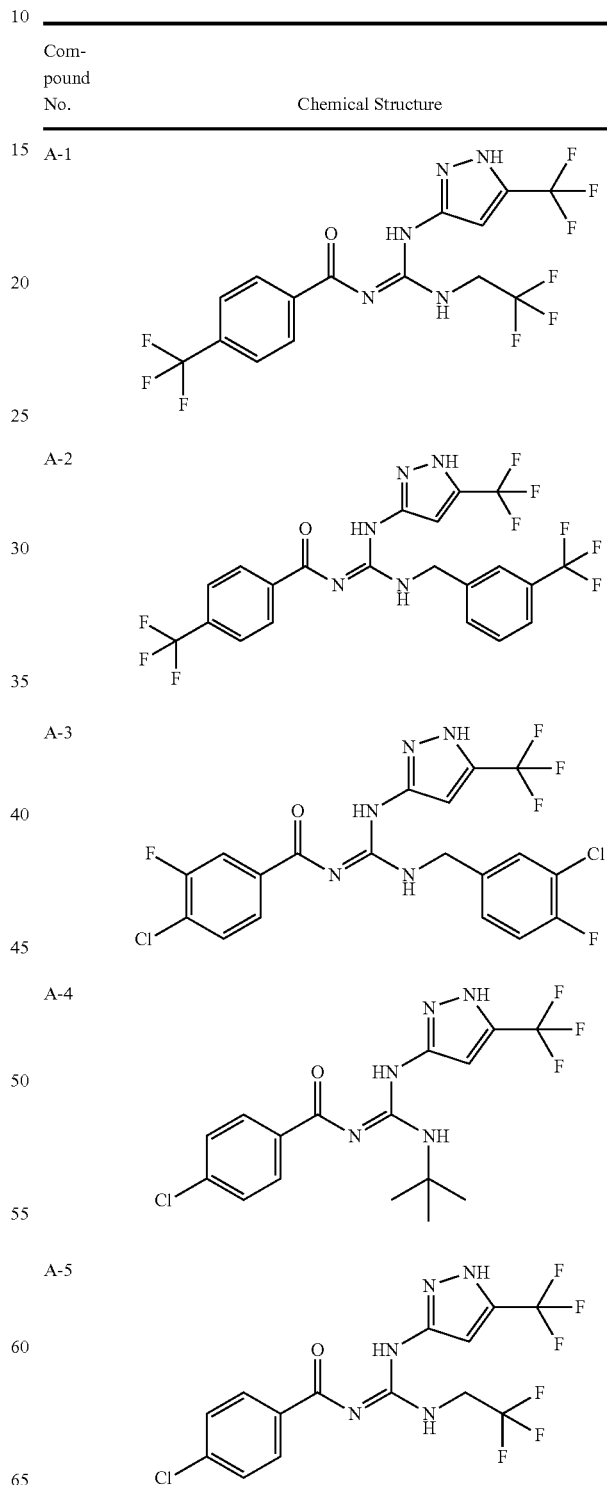
342

n is 1, 2, or 3;

m represents independently for each occurrence 1, 2, 3, 4, or 5; and

p represents independently for each occurrence 0, 1, or 2.

25. The compound of claim 1, wherein the compound is one of the following or a pharmaceutically acceptable salt thereof:



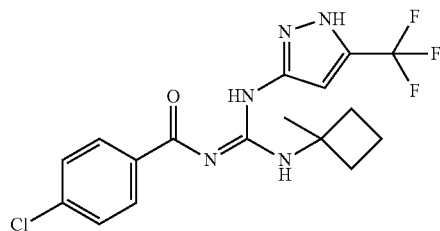
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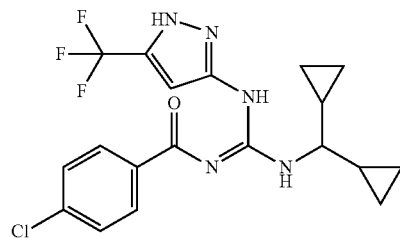
Compound  
No.

Chemical Structure

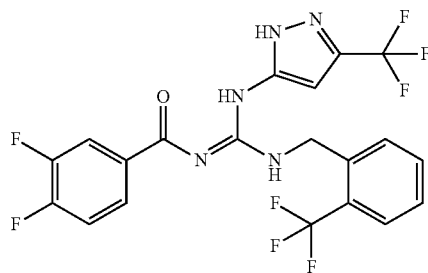
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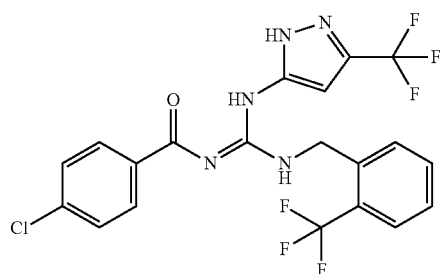
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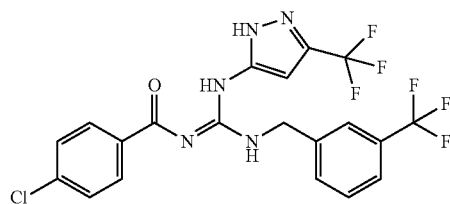
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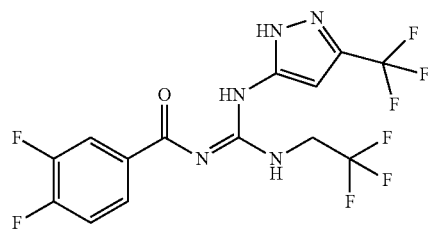
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A-10



A-11



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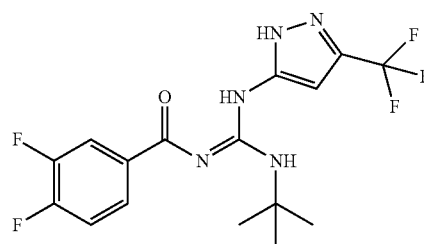
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Compound  
No.

Chemical Structure

A-12

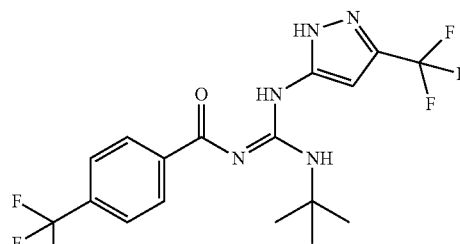
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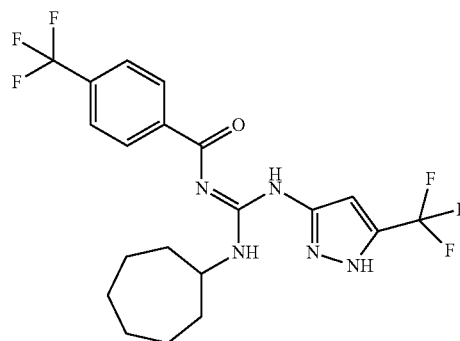
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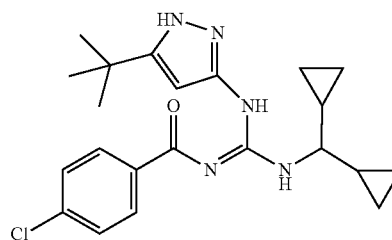
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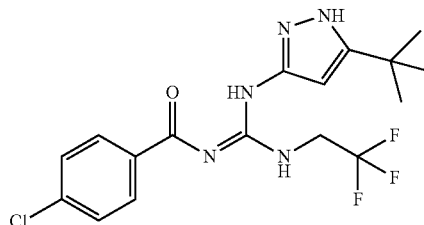
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A-16

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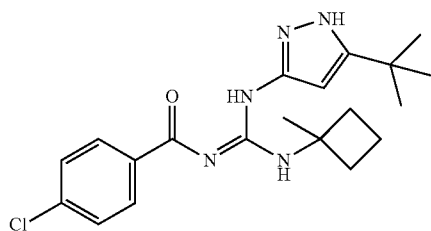
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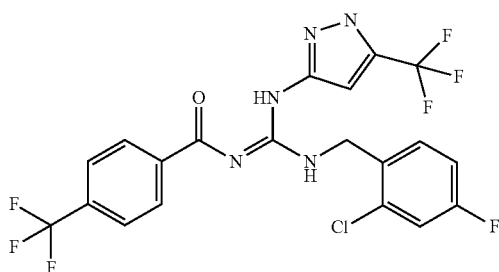
Com-  
pound  
No.

Chemical Structure

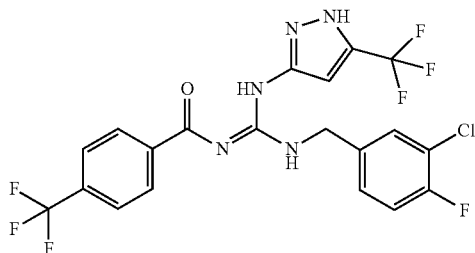
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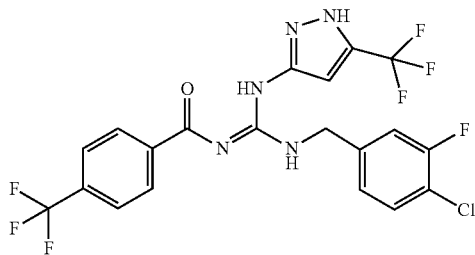
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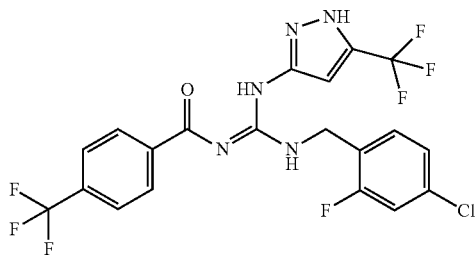
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A-20



A-21



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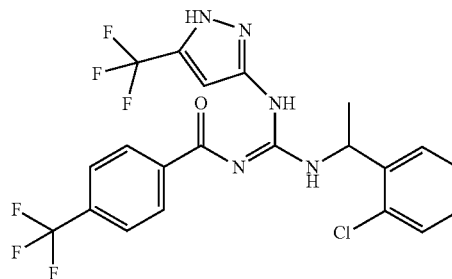
Com-  
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No.

Chemical Structure

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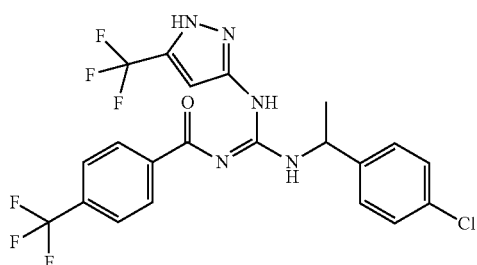
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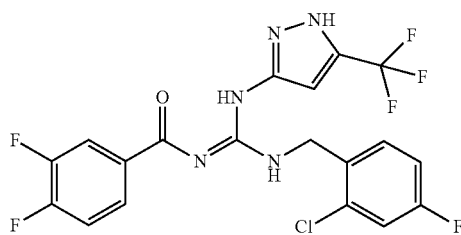
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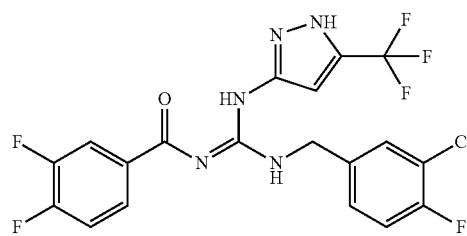
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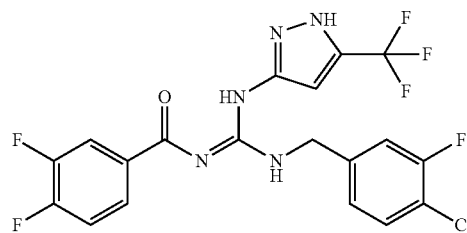
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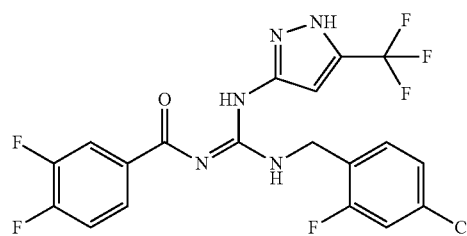
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A-27

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Compound No.	Chemical Structure
A-28	
A-29	
A-30	
A-31	
A-32	
A-33	

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Compound No.	Chemical Structure
A-34	
A-35	
A-36	
A-37	
A-39	



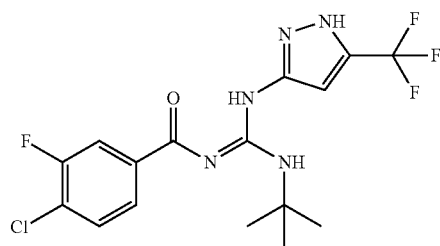
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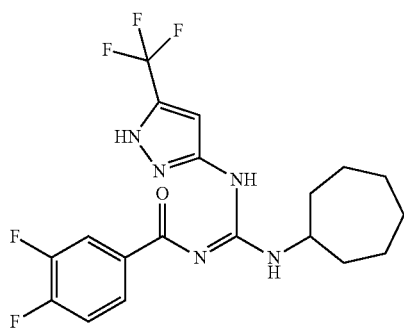
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No.

Chemical Structure

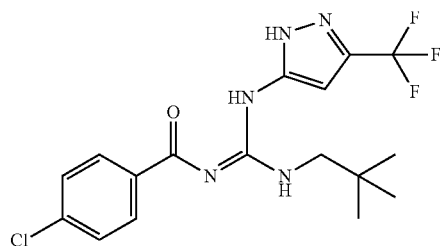
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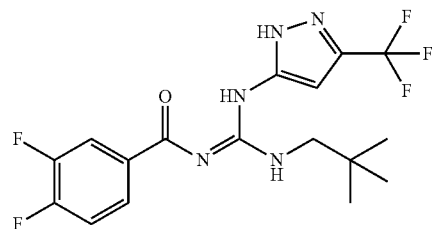
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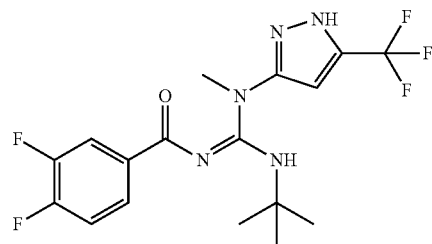
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A-43



A-44



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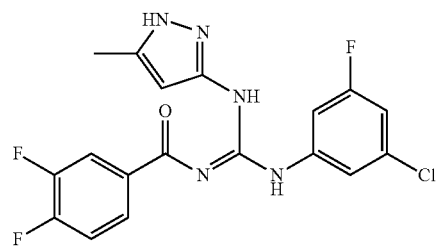
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Com-  
pound  
No.

Chemical Structure

A-45

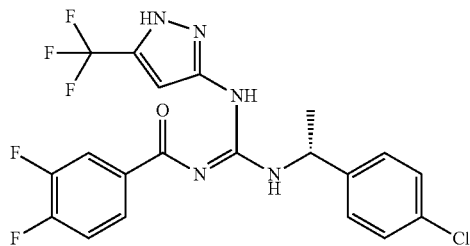
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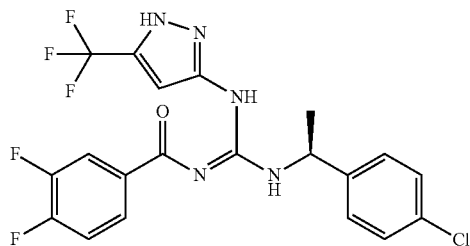
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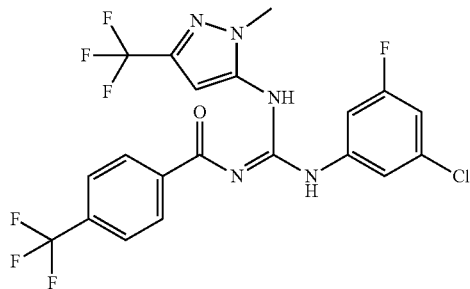
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A-48

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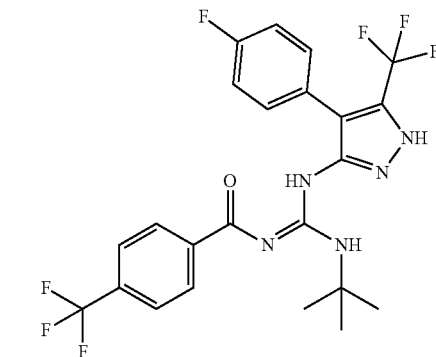


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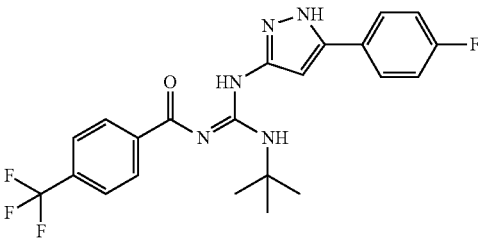
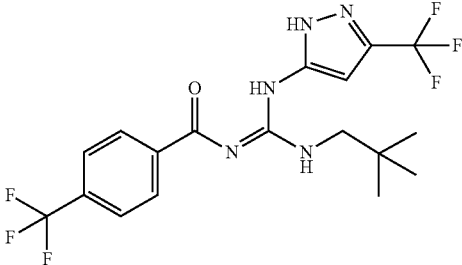
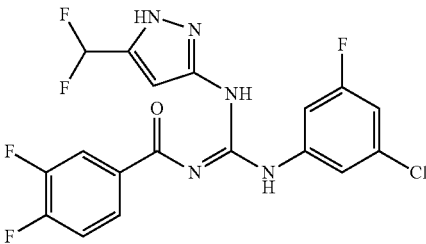
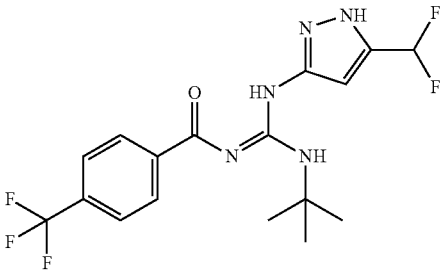
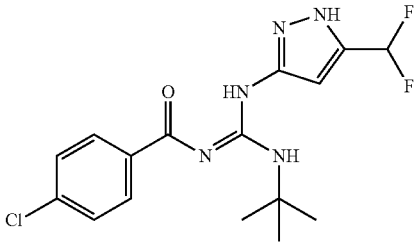
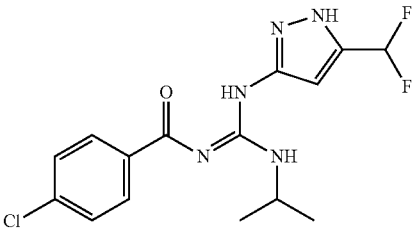


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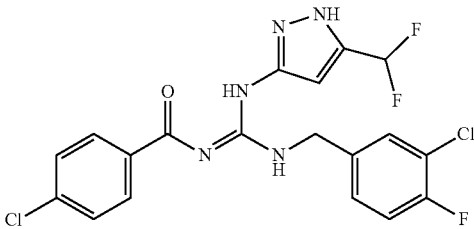
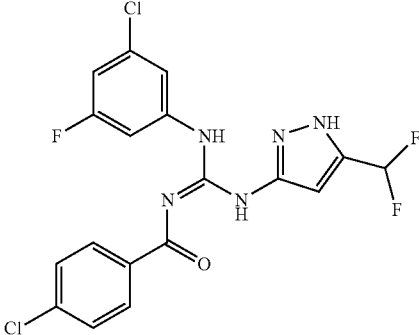
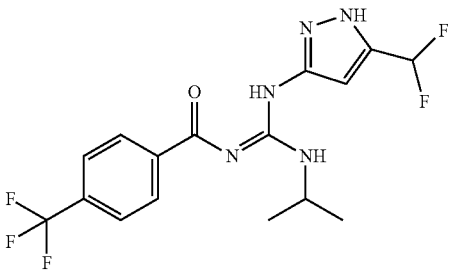
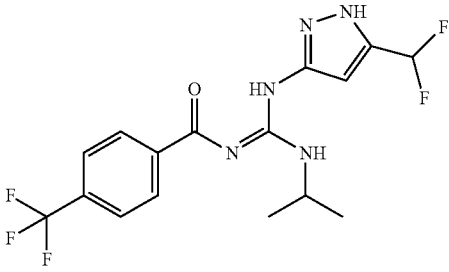
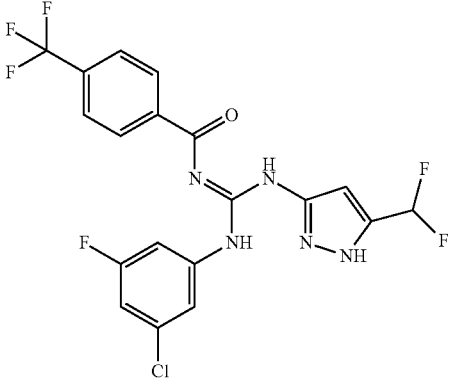
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Compound No.	Chemical Structure
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A-51	
A-52	
A-53	
A-54	
A-55	

352

-continued

Compound No.	Chemical Structure
A-56	
A-57	
A-58	
A-59	
A-60	

353

-continued

Compound No.	Chemical Structure
A-61	
A-62	
A-63	
A-64	
A-65	
A-66	

354

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Compound No.	Chemical Structure
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A-68	
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A-70	
A-71	
A-72	

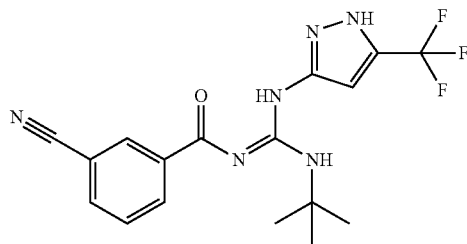
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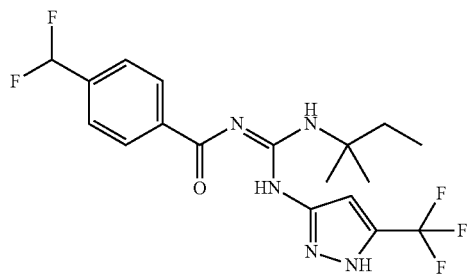
Compound  
No.

Chemical Structure

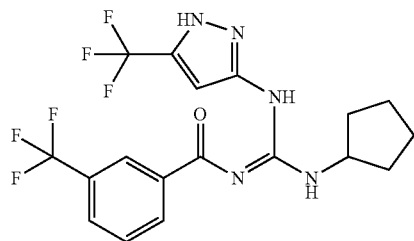
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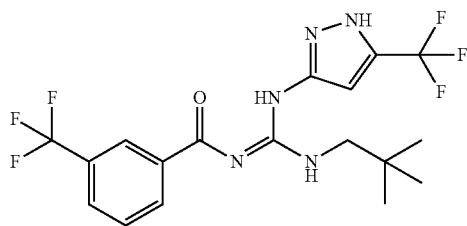
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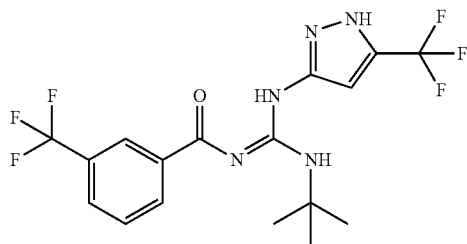
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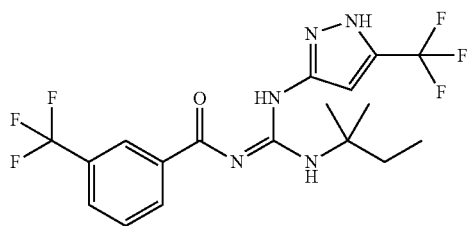
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A-77



A-78



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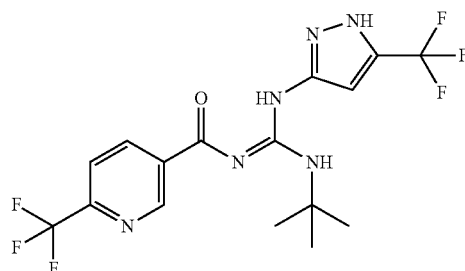
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Compound  
No.

Chemical Structure

A-79

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A-80

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A-81

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A-82

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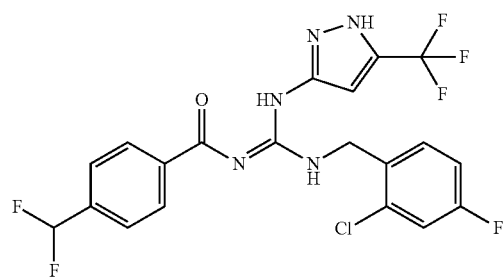
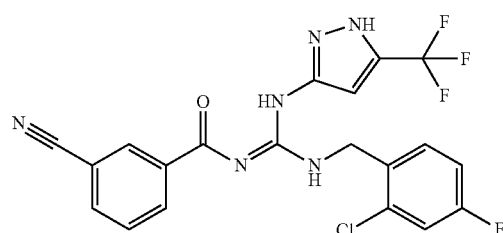
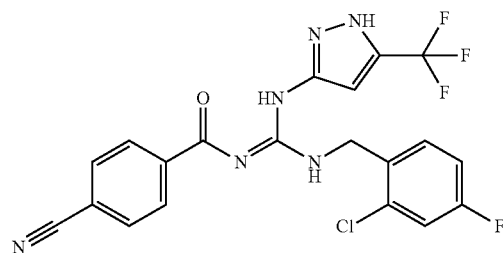
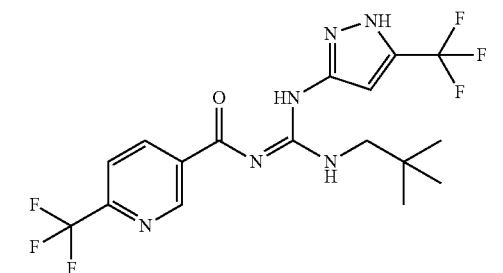
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A-83

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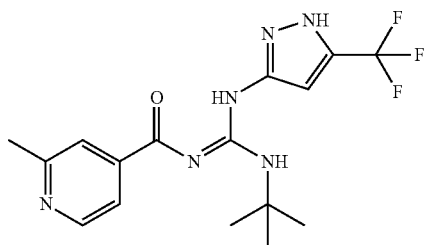
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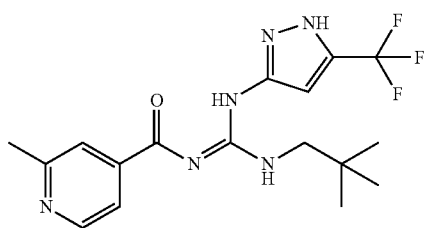
Com-  
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No.

Chemical Structure

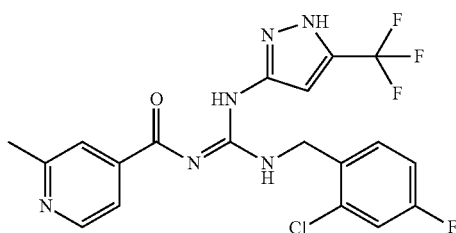
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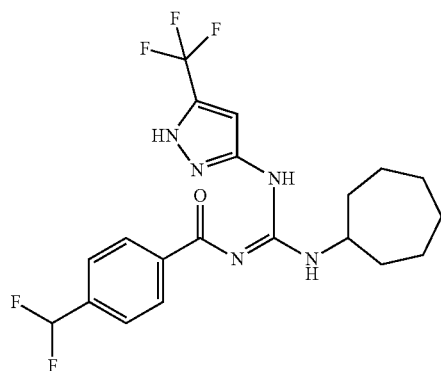
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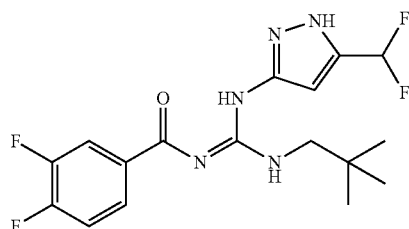
A-86



A-87



A-88



358

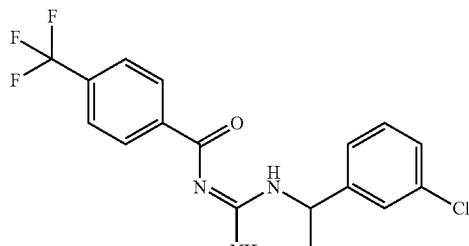
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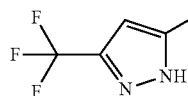
Chemical Structure

A-89

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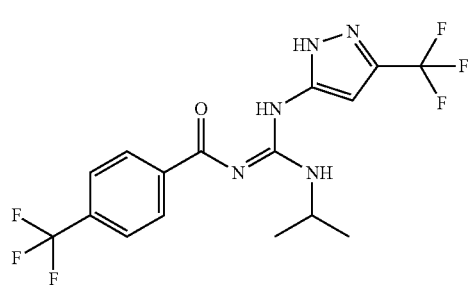


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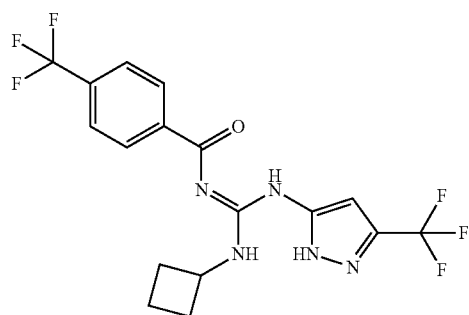
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A-91

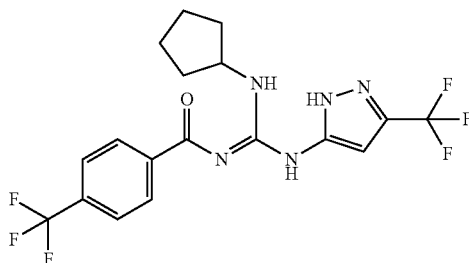
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45 A-92

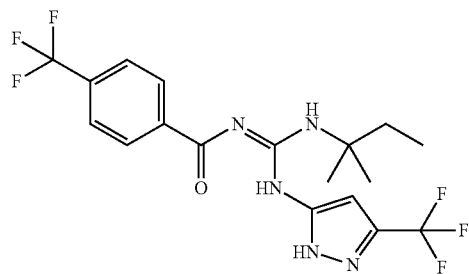
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A-93

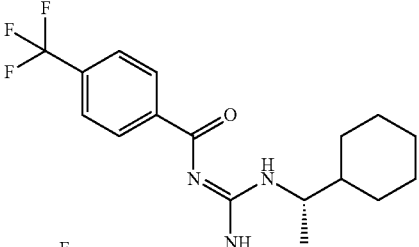
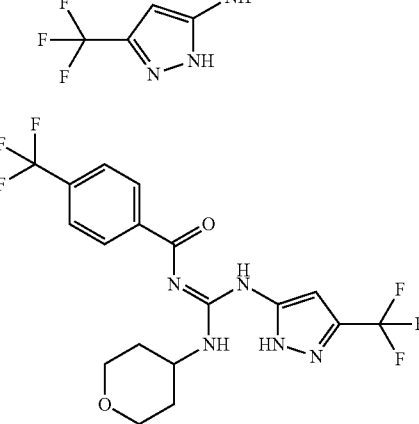
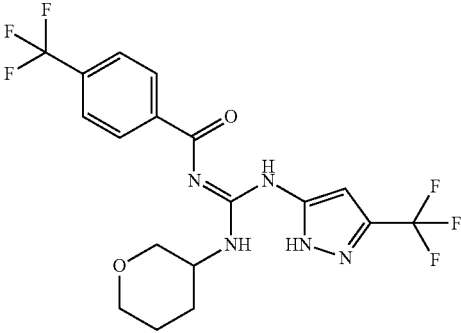
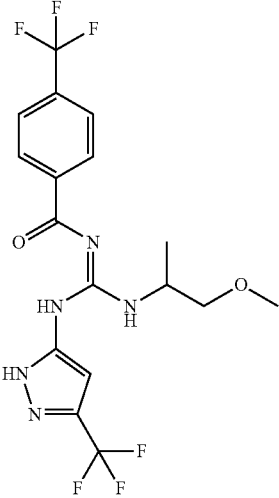
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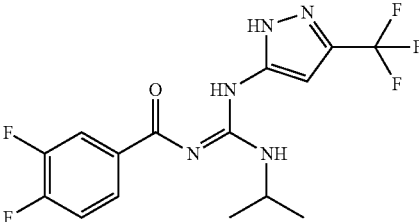
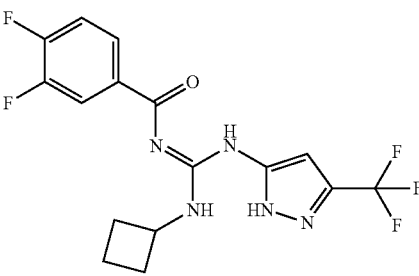
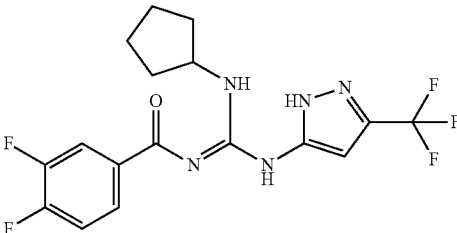
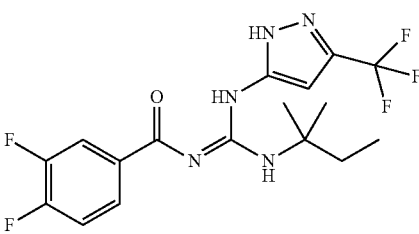
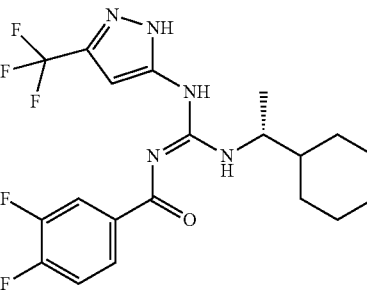
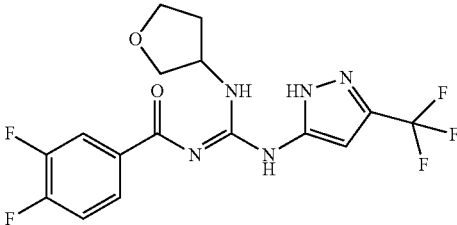
359

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Compound No.	Chemical Structure
A-94	
A-95	
A-96	
A-97	

360

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Compound No.	Chemical Structure
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A-99	
A-100	
A-101	
A-102	
A-103	

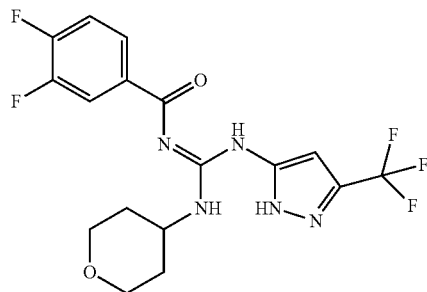
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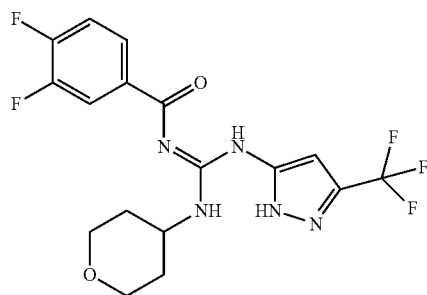
Com-  
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No.

Chemical Structure

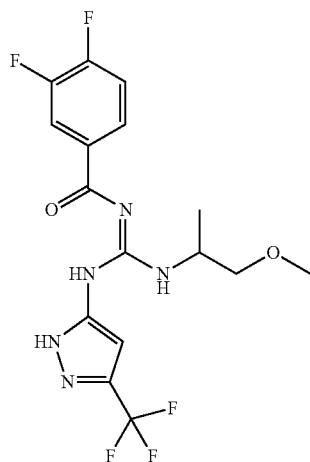
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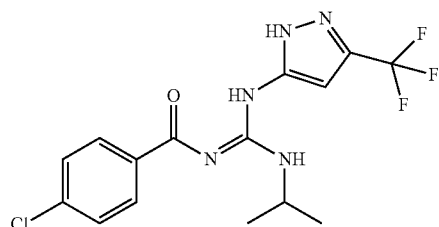
A-105



A-106



A-107



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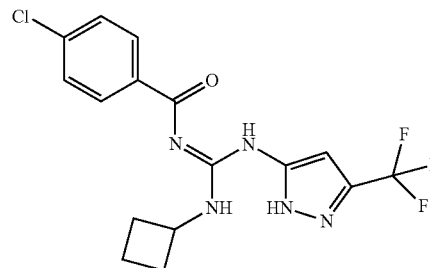
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Com-  
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No.

Chemical Structure

A-108

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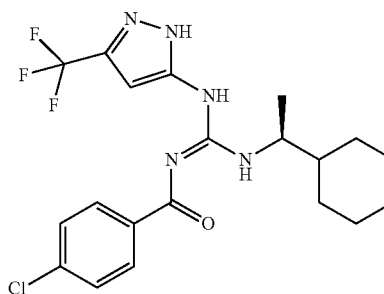
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A-109

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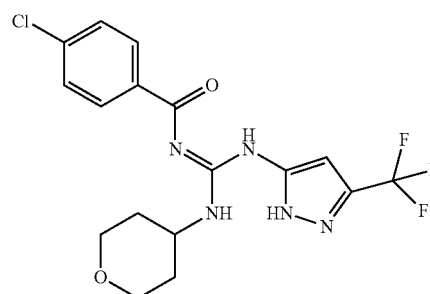


A-110

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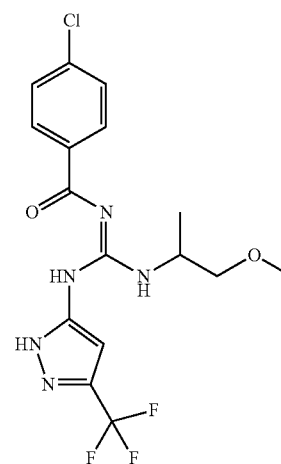
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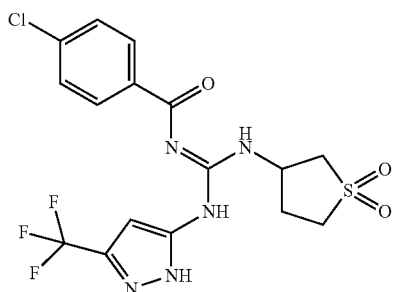
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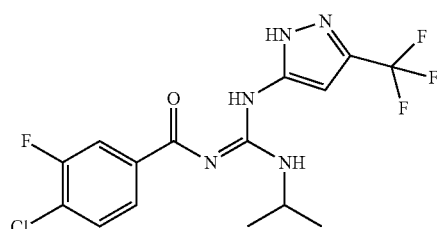
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Chemical Structure

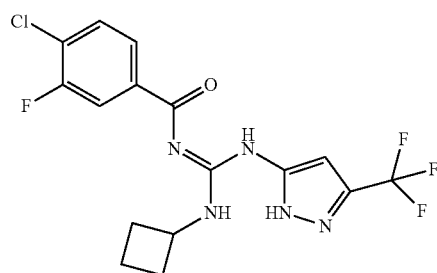
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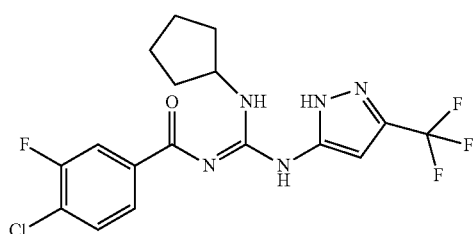
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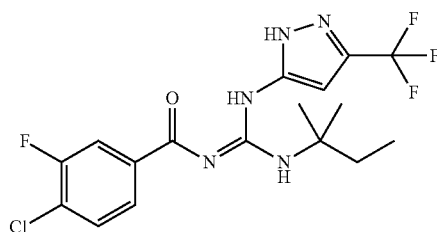
A-114



A-115



A-116



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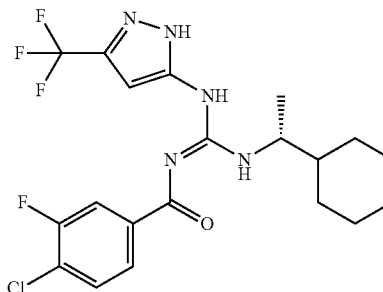
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No.

Chemical Structure

A-117

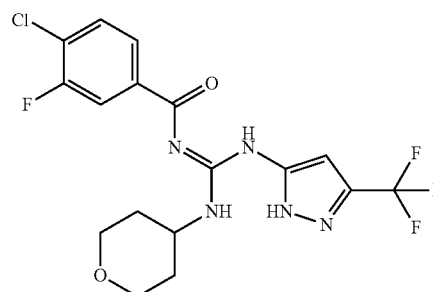
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A-118

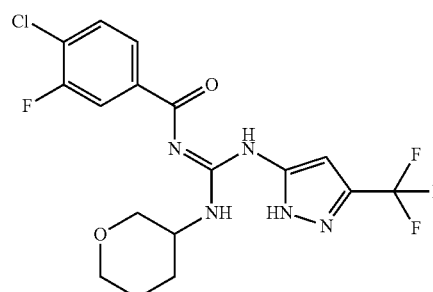
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A-119

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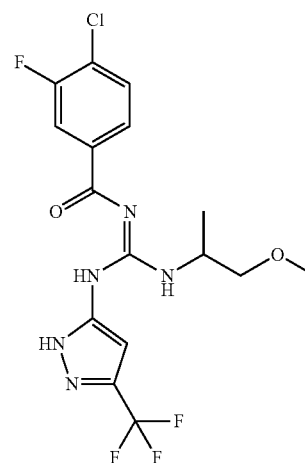


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A-120

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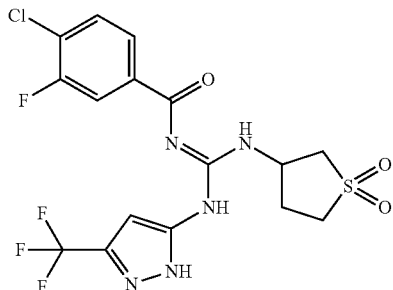
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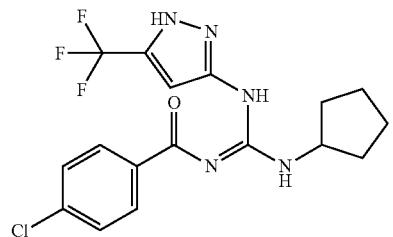
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Chemical Structure

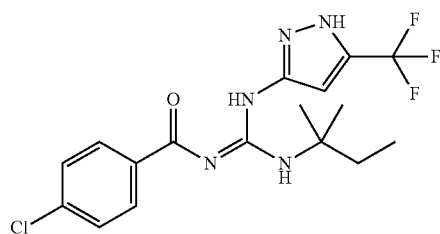
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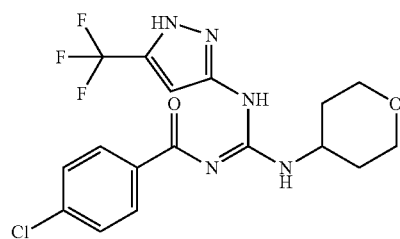
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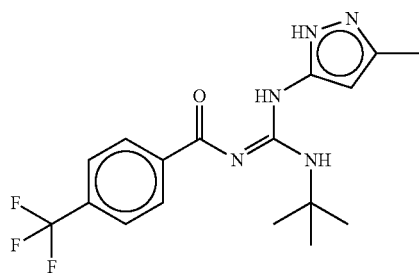
A-123



A-124



A-125



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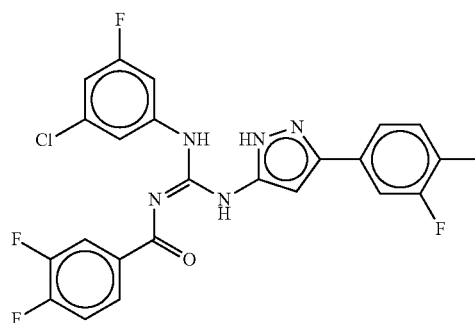
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Com-  
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No.

Chemical Structure

A-126

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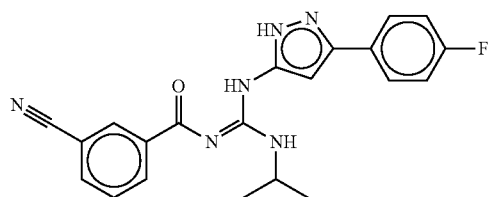


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A-127

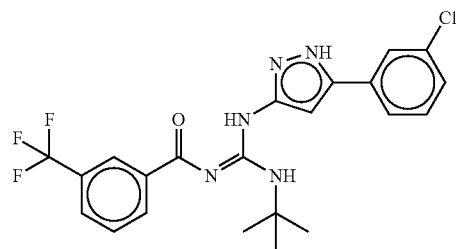
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A-128

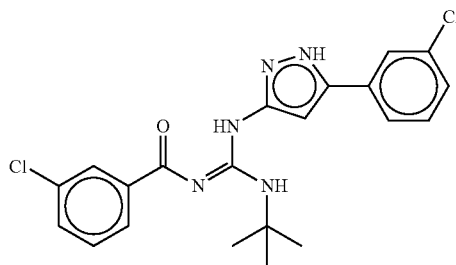
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A-129

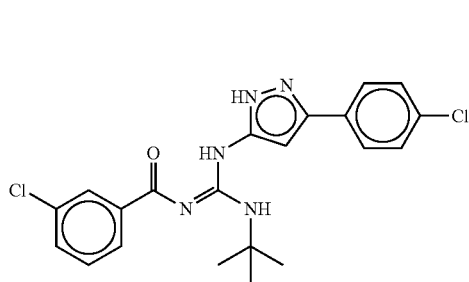
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367

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Compound No.	Chemical Structure
A-131	
A-132	
A-133	
A-134	
A-135	
A-136	

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Compound No.	Chemical Structure
A-137	
A-138	
A-139	
A-140	
A-141	
A-142	

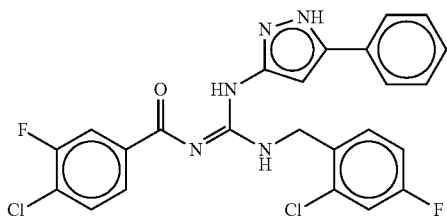
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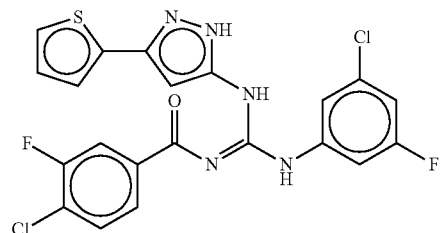
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No.

Chemical Structure

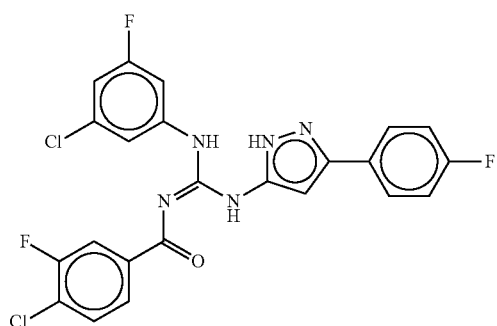
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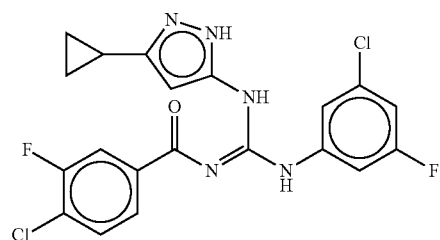
A-144



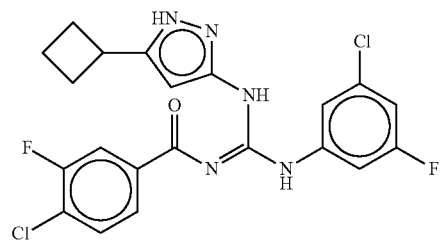
A-145



A-146



A-147



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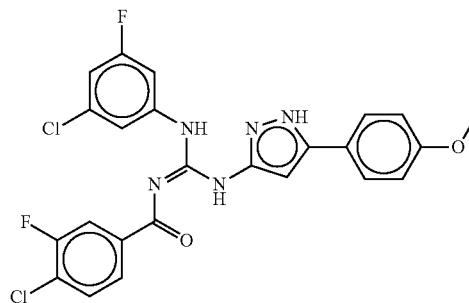
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Chemical Structure

A-148

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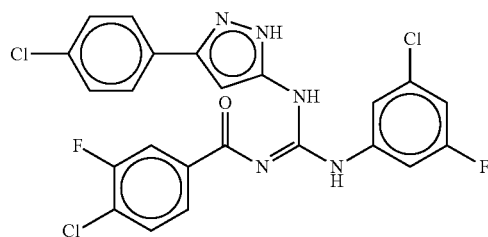


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A-149

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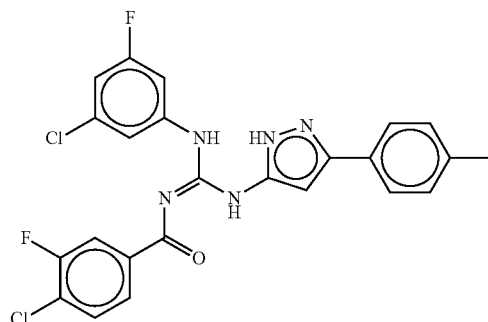


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A-150

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A-151

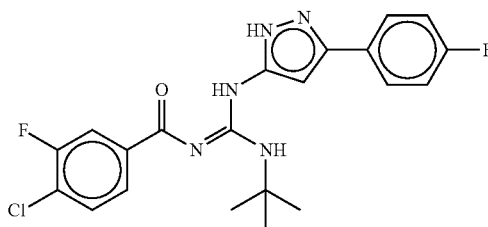
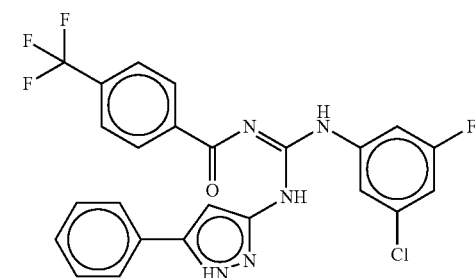
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A-152

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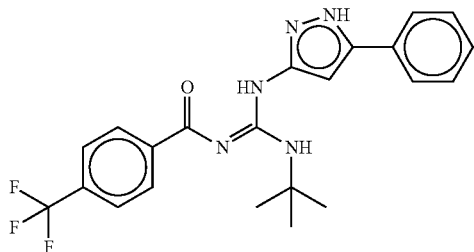
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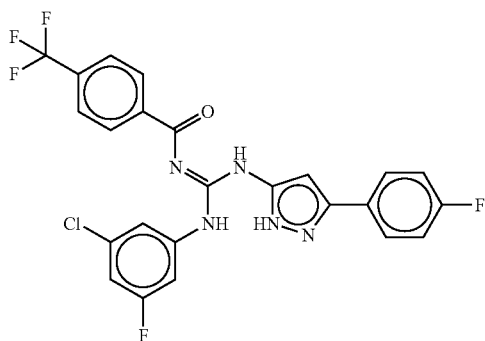
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Chemical Structure

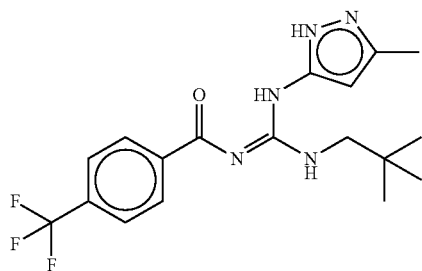
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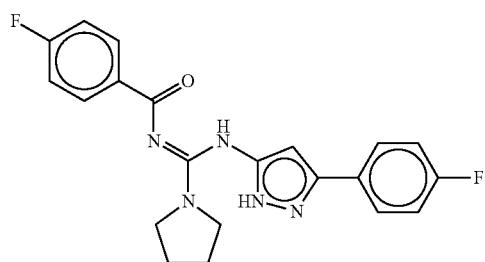
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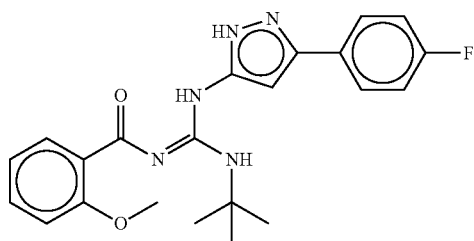
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A-156



A-157



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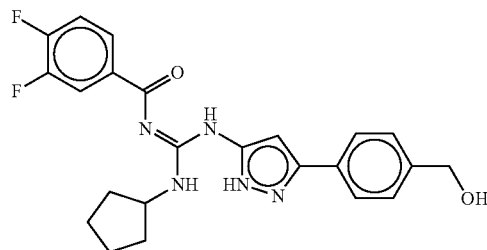
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Com-  
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Chemical Structure

A-158

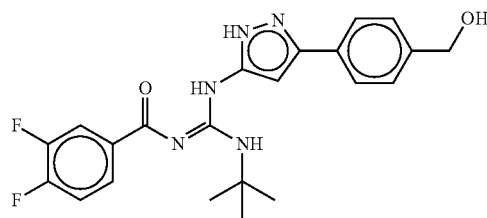
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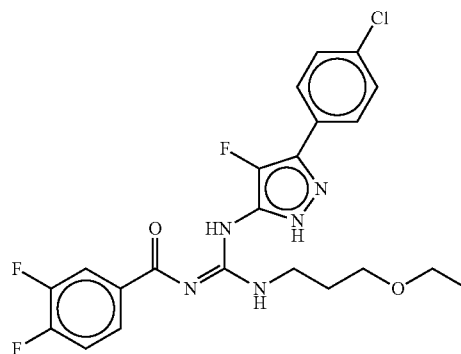
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A-160

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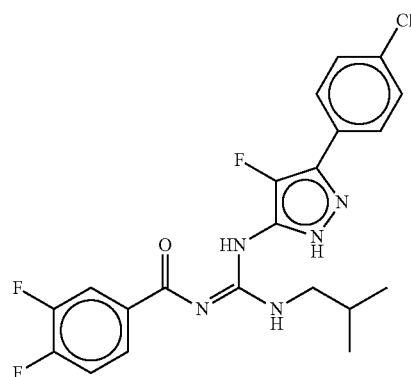


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A-161

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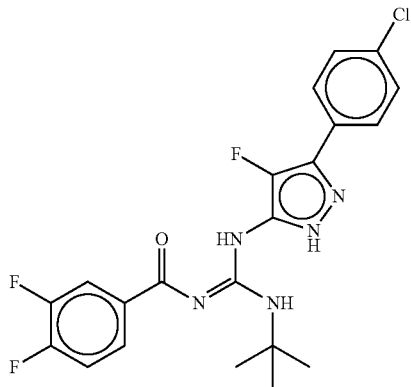
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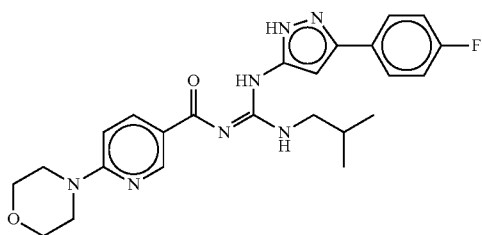
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Chemical Structure

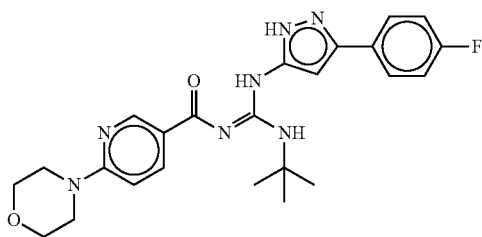
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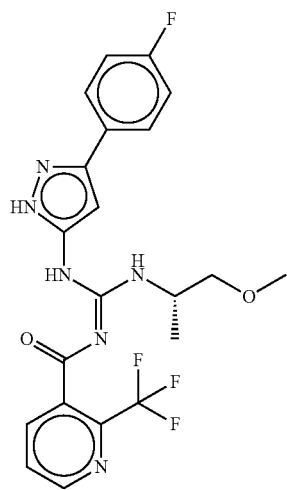
A-163



A-164



A-165



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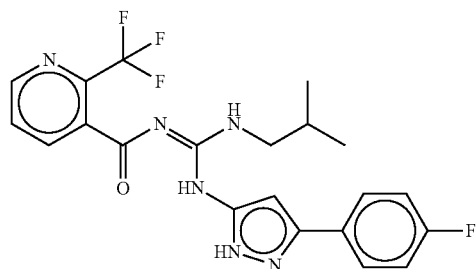
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Com-  
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Chemical Structure

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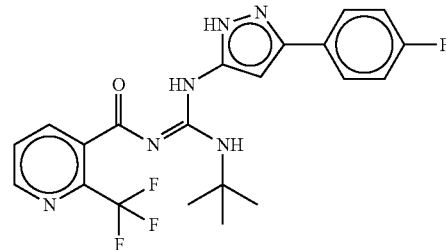
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A-167

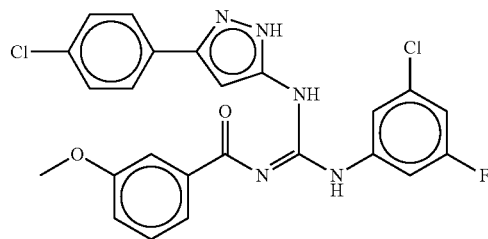
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A-168

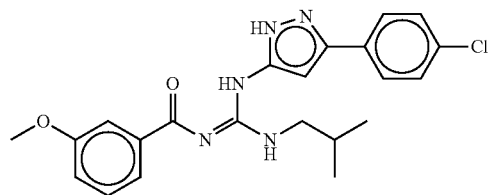
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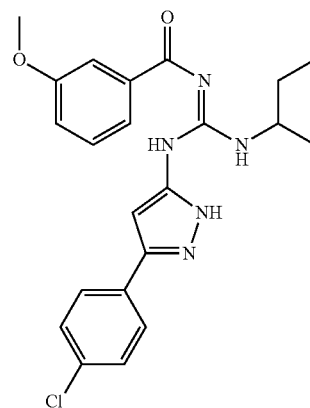
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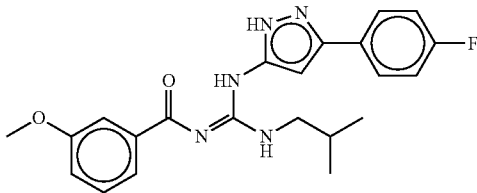
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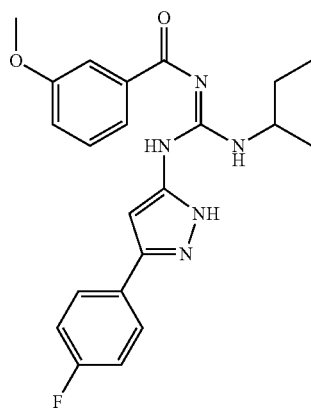
Compound  
No.

Chemical Structure

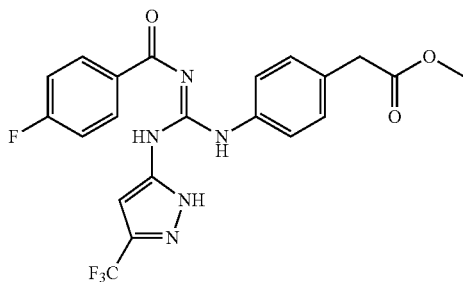
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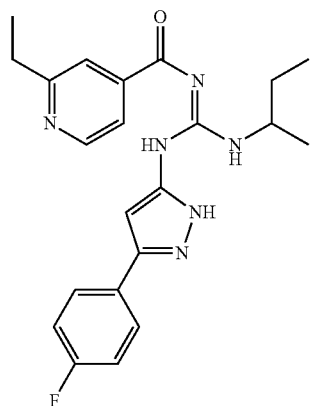
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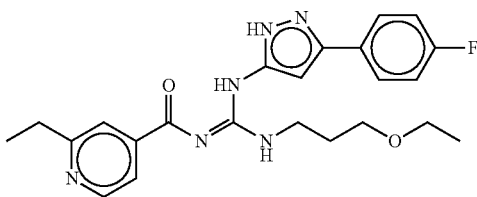
A-173



A-174



A-175



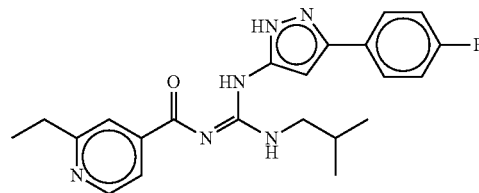
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Compound  
No.

Chemical Structure

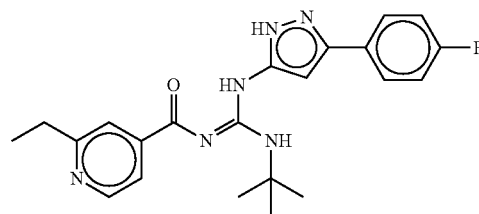
A-176



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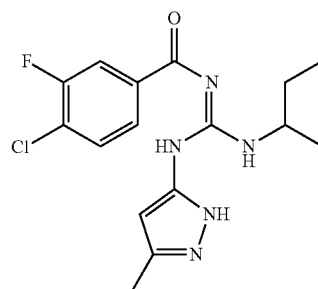
A-177



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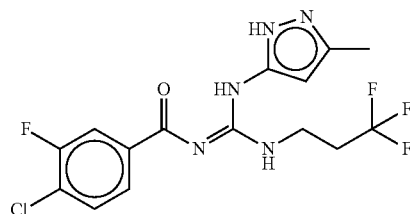
A-178



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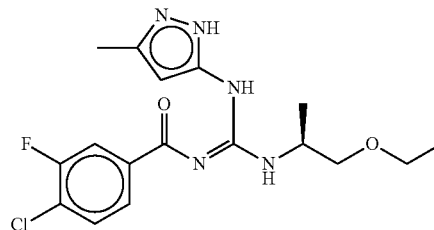
A-179



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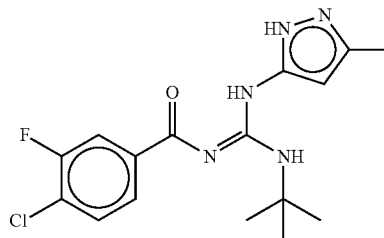
A-180



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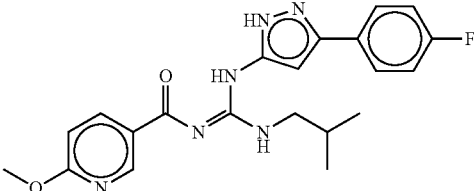
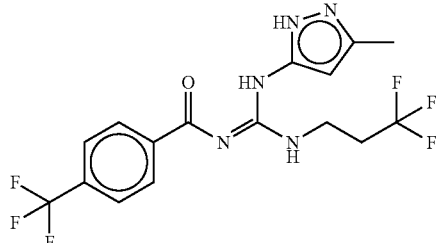
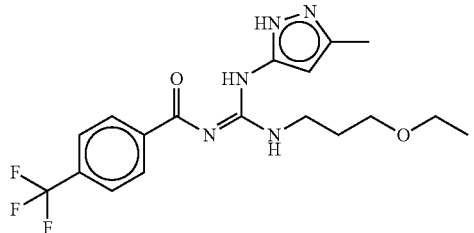
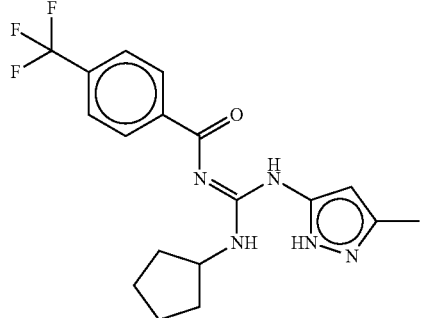
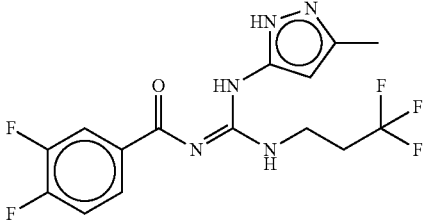
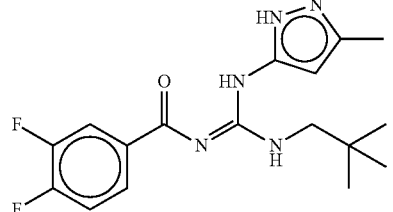
A-181



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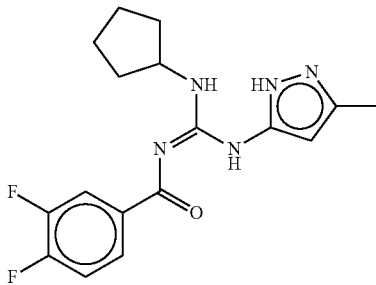
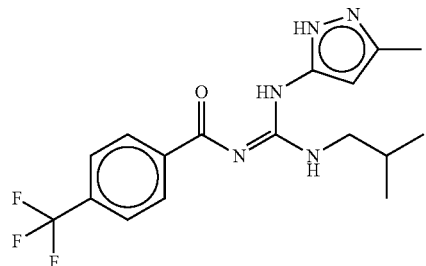
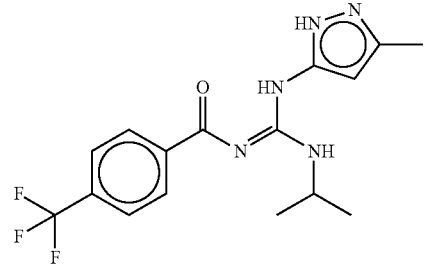
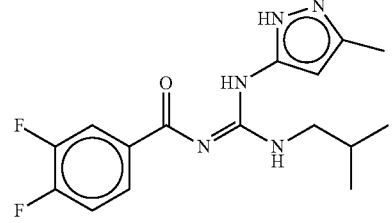
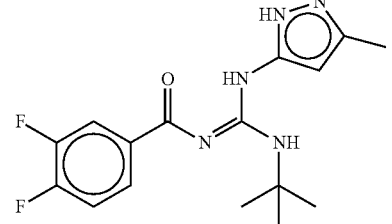
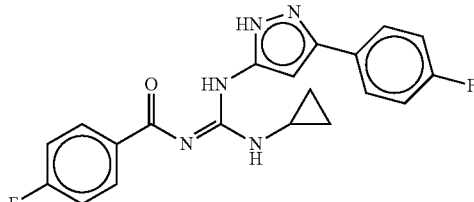
377

-continued

Compound No.	Chemical Structure
A-182	
A-183	
A-184	
A-185	
A-186	
A-187	

378

-continued

Compound No.	Chemical Structure
A-188	
A-189	
A-190	
A-191	
A-192	
A-193	

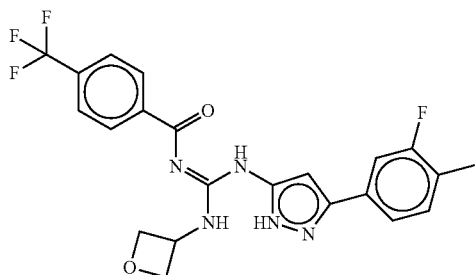
379

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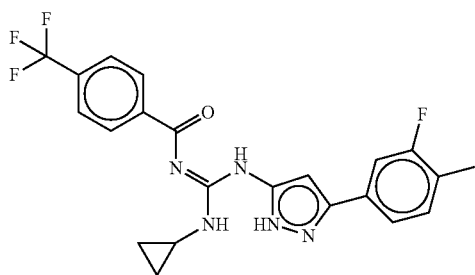
Com-  
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No.

Chemical Structure

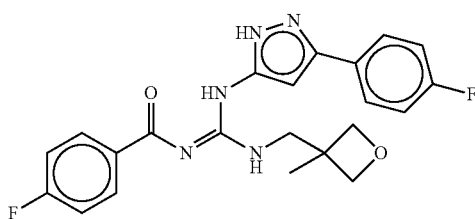
A-194



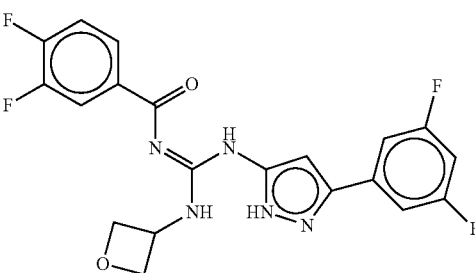
A-195



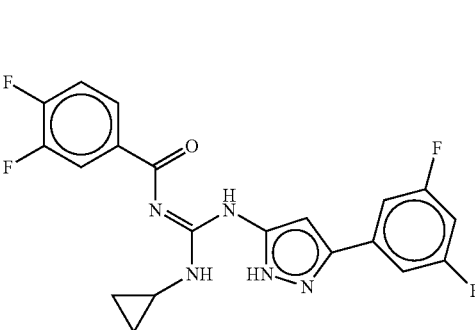
A-196



A-197



A-198



380

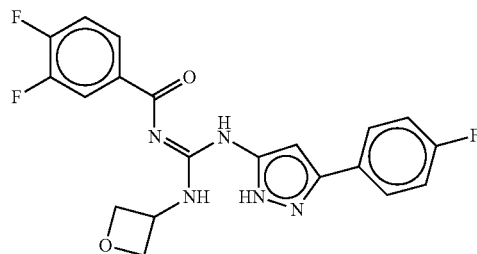
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Com-  
pound  
No.

Chemical Structure

A-199

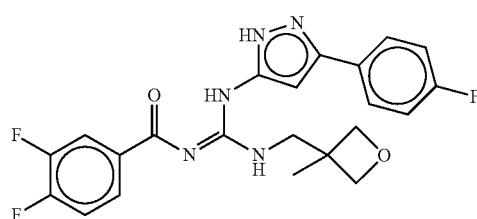
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A-200

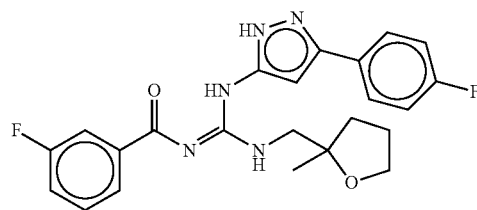
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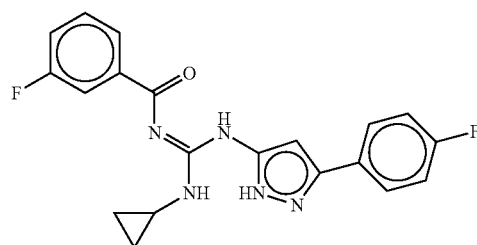
A-201

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A-202

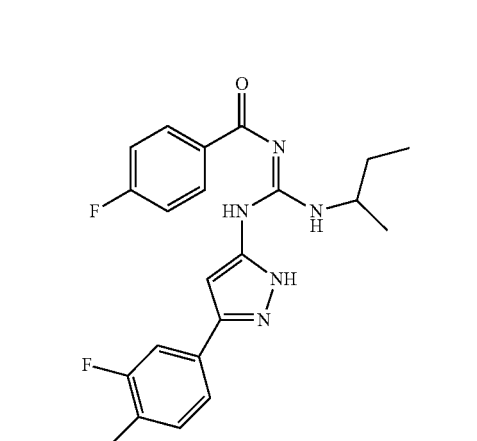
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A-203

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382  
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Compound No.	Chemical Structure
A-209	
A-210	
A-211	
A-212	
A-213	
A-214	

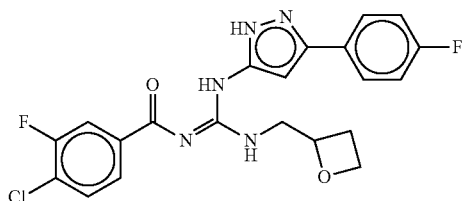
**383**

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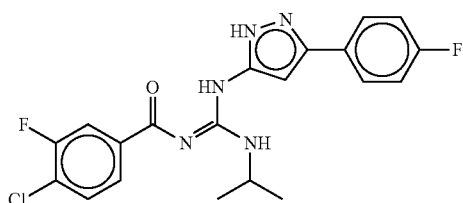
Com-  
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No.

Chemical Structure

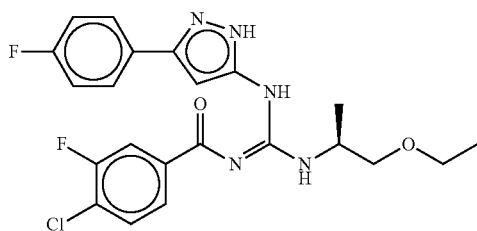
A-215



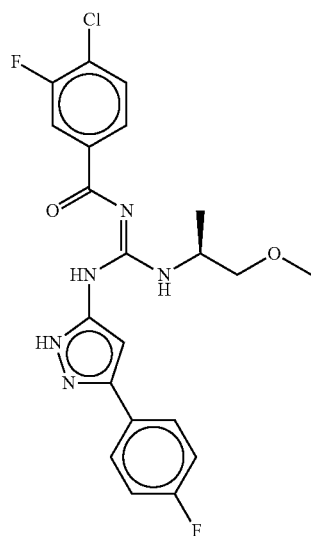
A-216



A-217



A-218

**384**

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Com-  
pound  
No.

Chemical Structure

A-219

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A-220

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A-221

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A-222

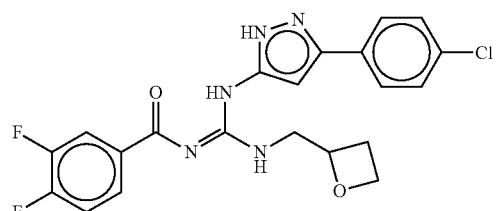
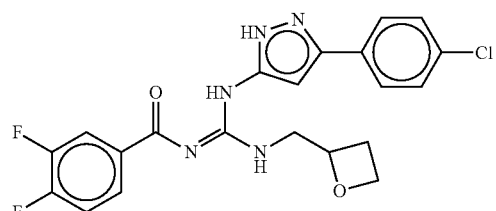
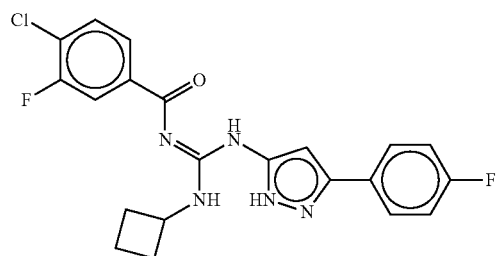
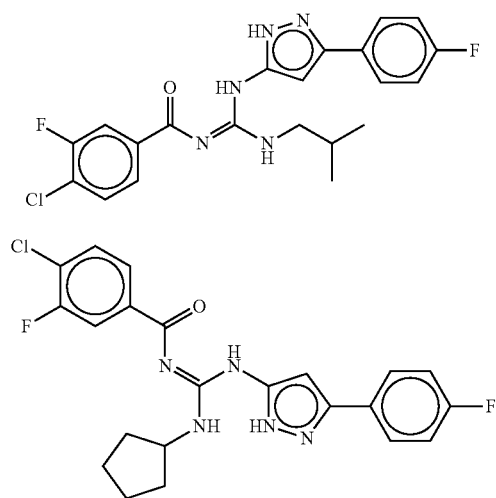
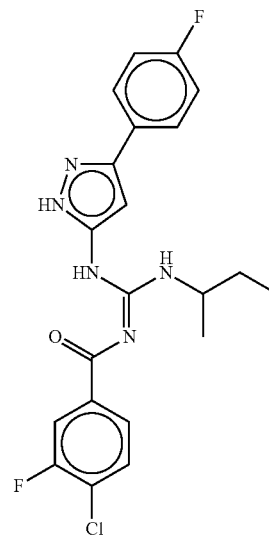
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A-223

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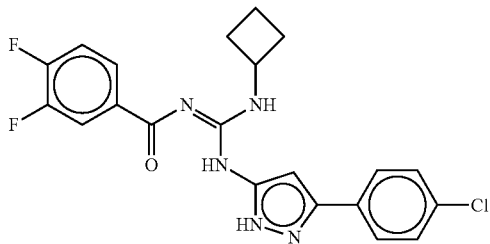
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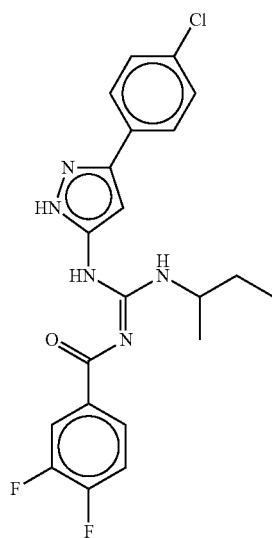
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Chemical Structure

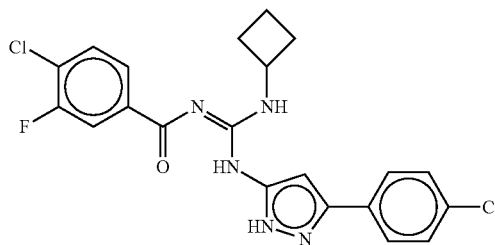
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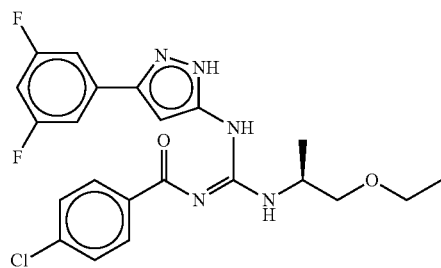
A-225



A-226



A-227

**386**

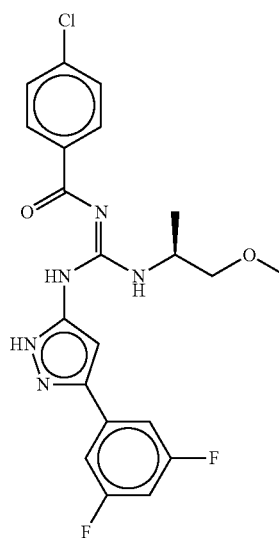
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Com-  
pound  
No.

Chemical Structure

A-228

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A-229

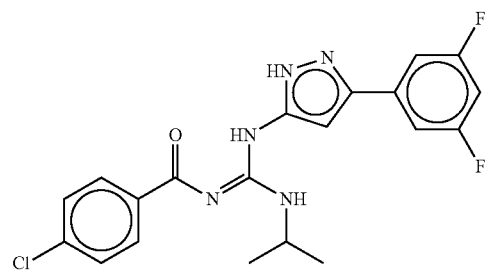
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A-230

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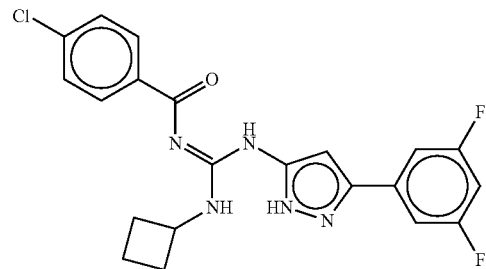


A-231

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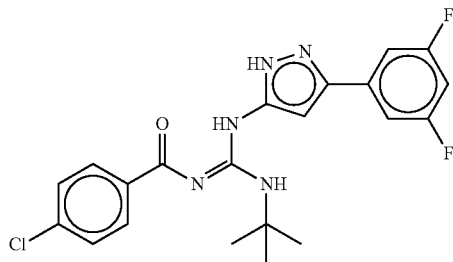
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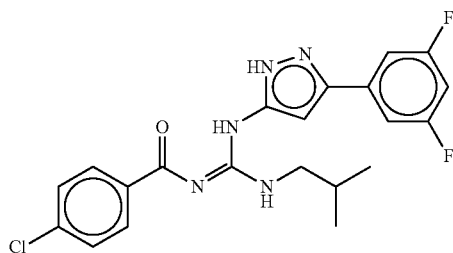
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Chemical Structure

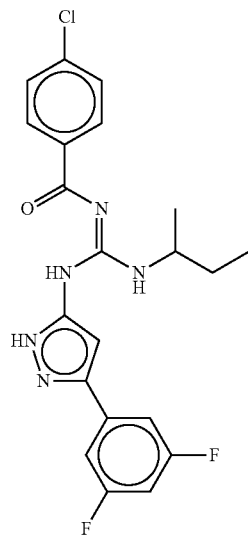
A-232



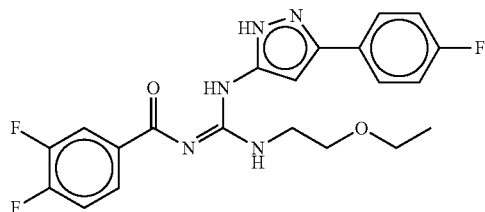
A-233



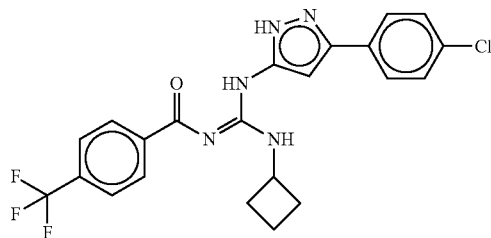
A-234



A-235



A-236

**388**

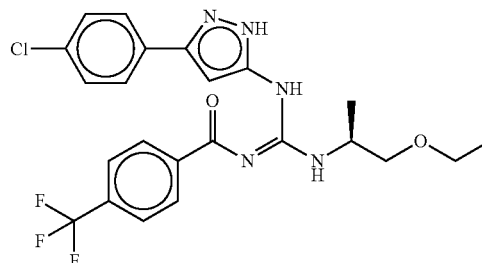
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No.

Chemical Structure

A-237

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A-238

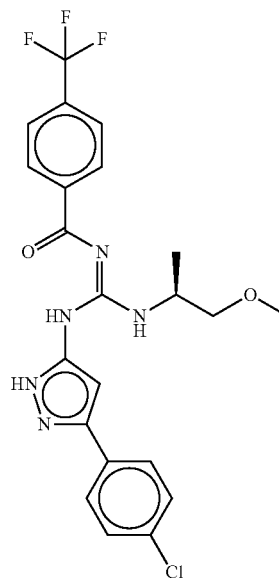
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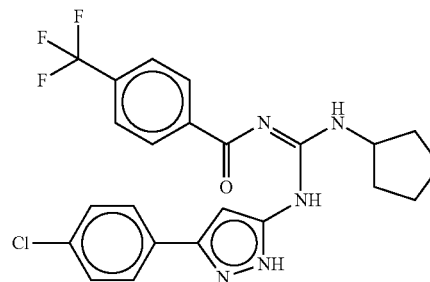
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A-239

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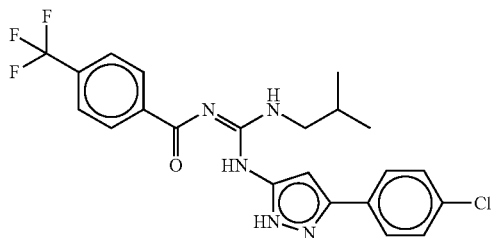


A-240

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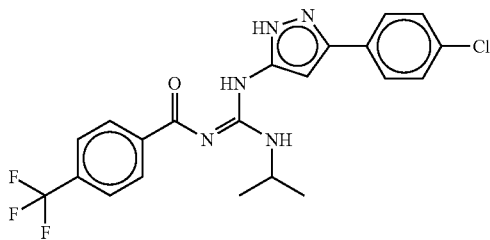
389

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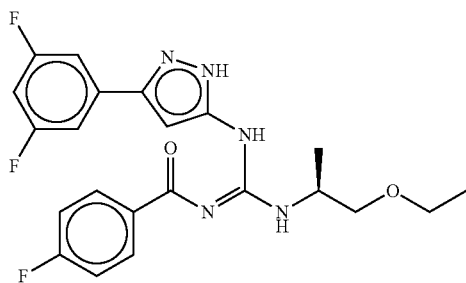
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No.

Chemical Structure

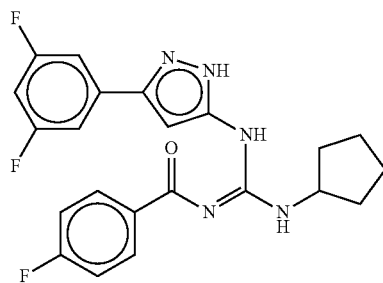
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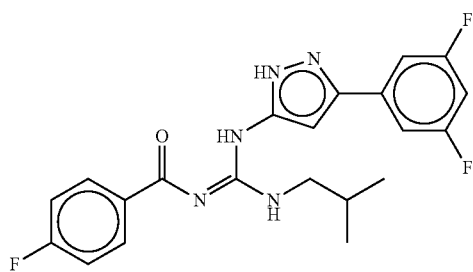
A-242



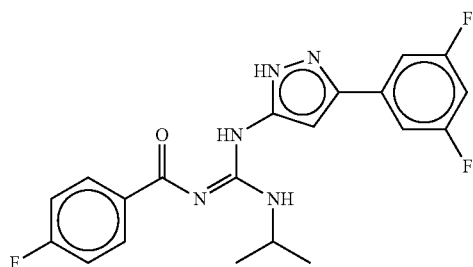
A-243



A-244



A-245



390

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Com-  
pound  
No.

Chemical Structure

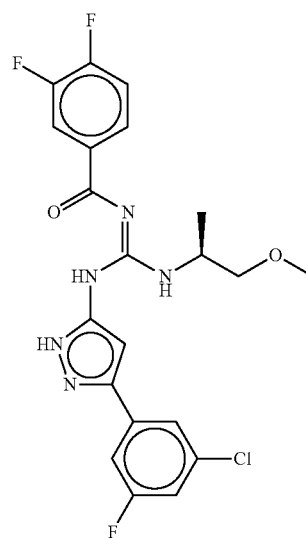
A-246

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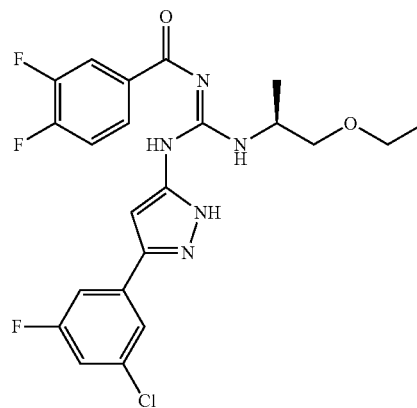


A-247

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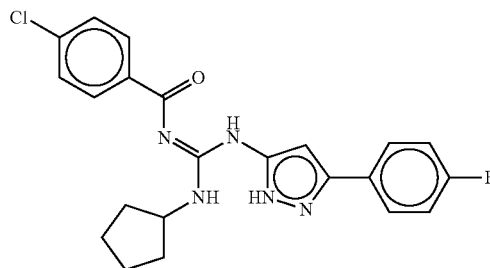


A-248

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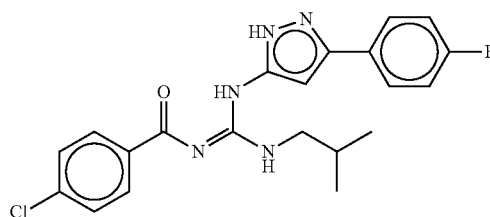
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A-249

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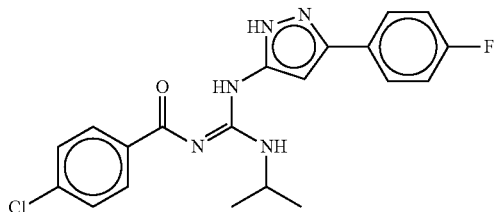
391

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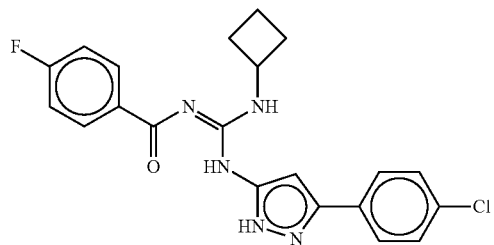
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Chemical Structure

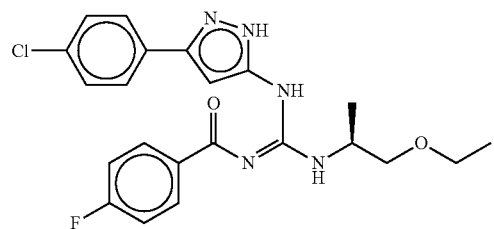
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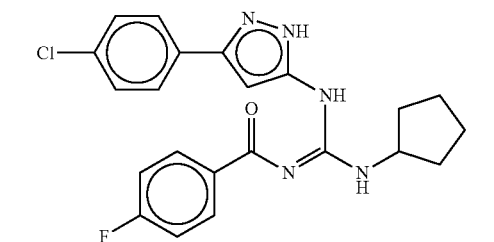
A-251



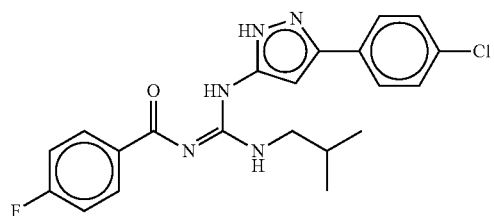
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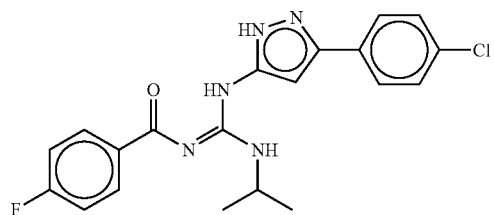
A-253



A-254



A-255



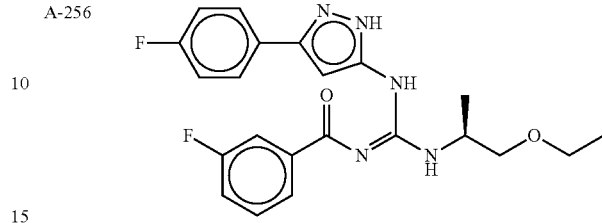
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Com-  
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No.

Chemical Structure

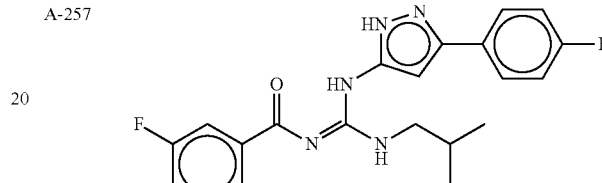
A-256



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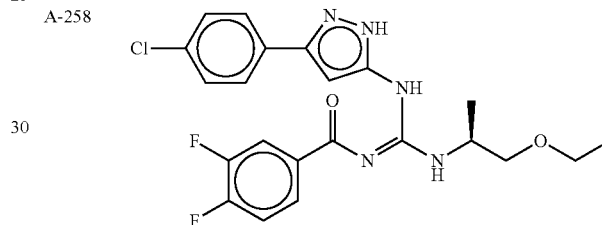
A-257



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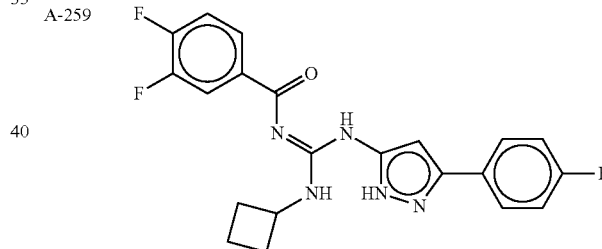
A-258



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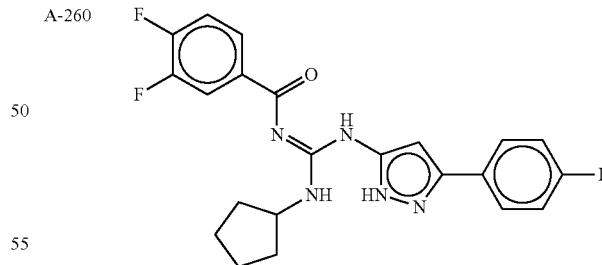
A-259



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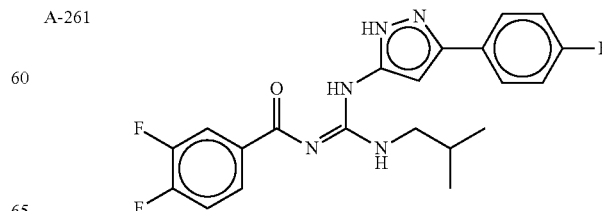
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A-261



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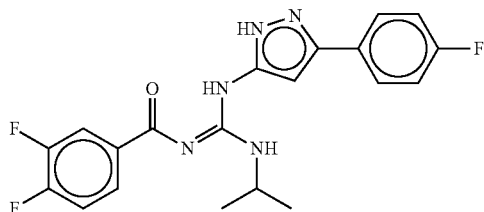
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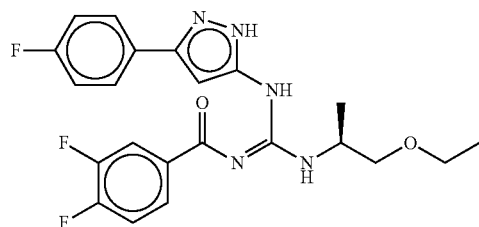
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Chemical Structure

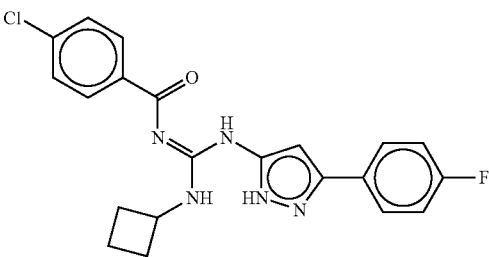
A-262



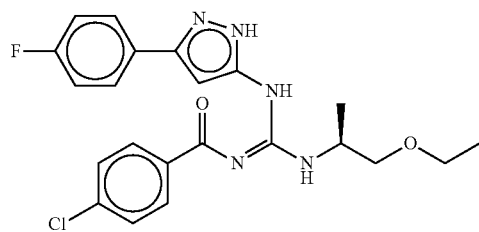
A-263



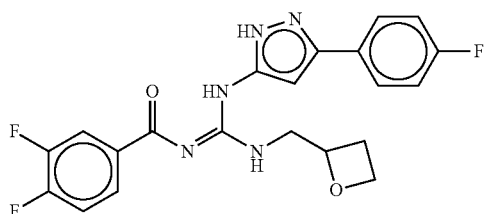
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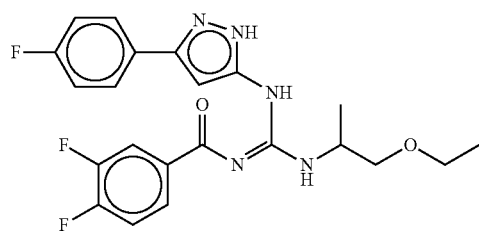
A-265



A-266



A-267



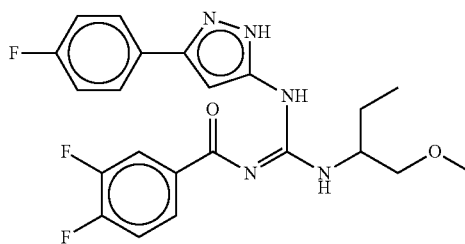
394

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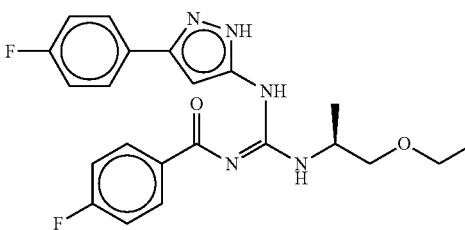
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Chemical Structure

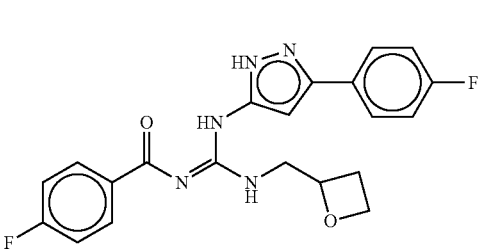
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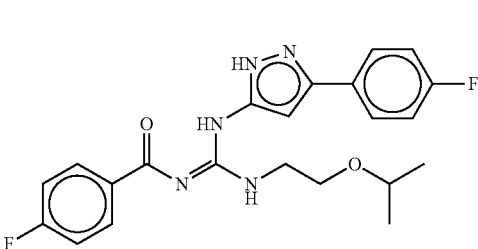
A-269



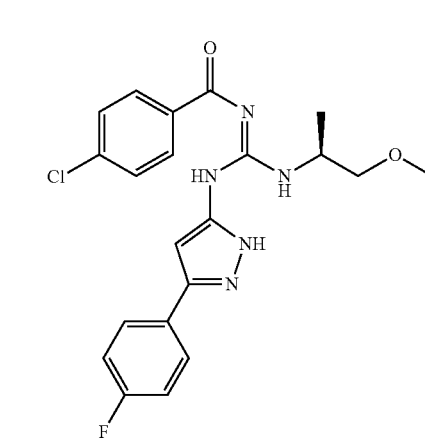
A-270



A-271



A-272



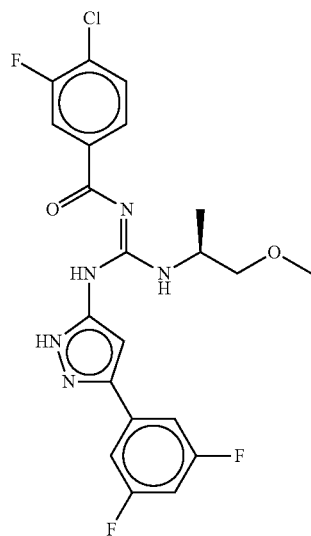
395

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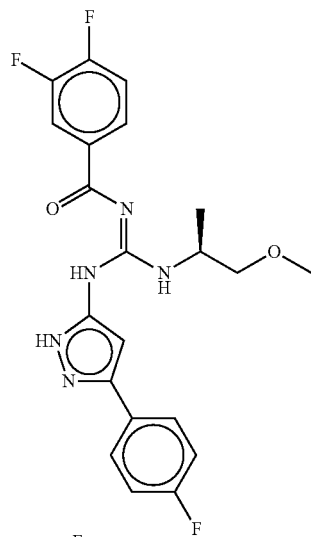
Compound  
No.

Chemical Structure

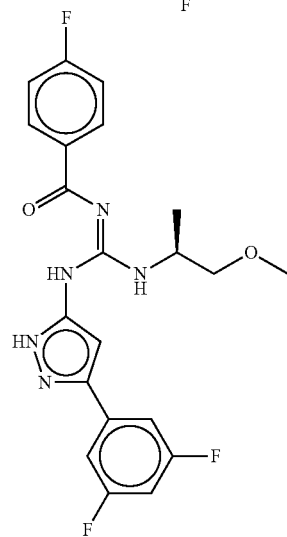
A-273



A-274



A-275



396

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Compound  
No.

Chemical Structure

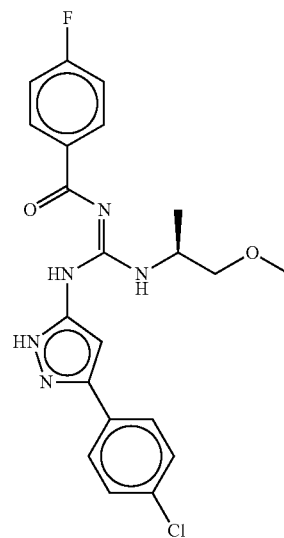
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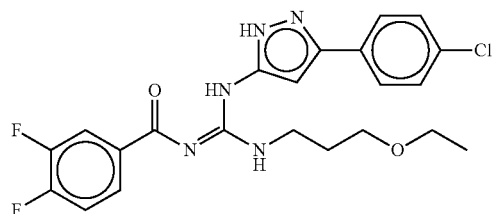
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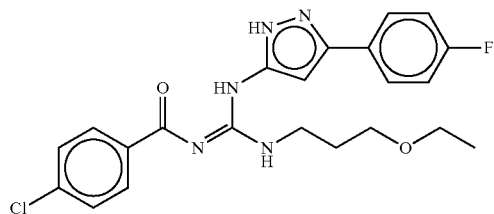
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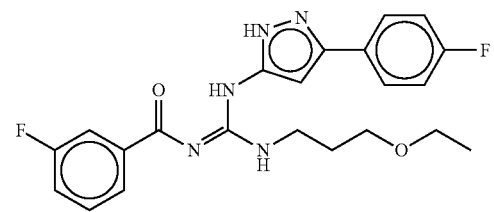
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A-279

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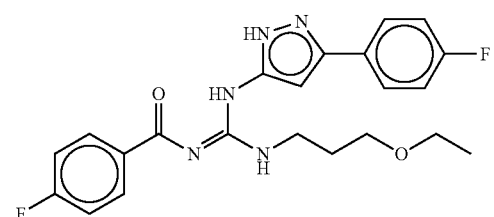
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A-280

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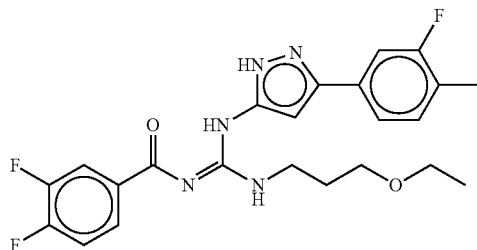
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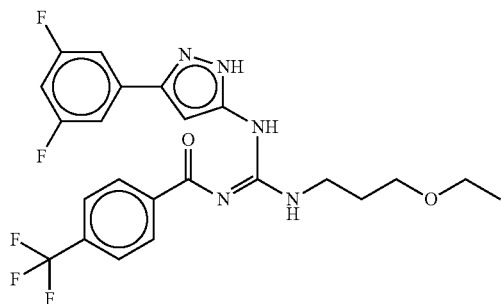
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No.

Chemical Structure

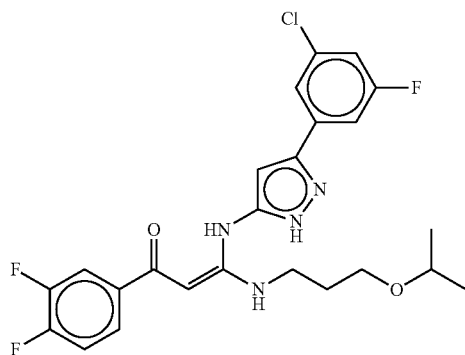
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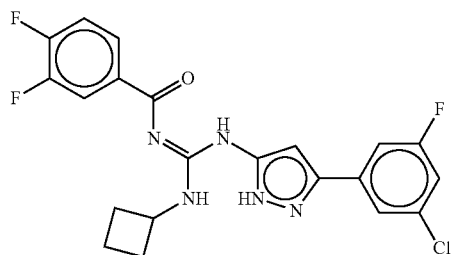
A-282



A-283



A-284



398

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Com-  
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No.

Chemical Structure

A-285

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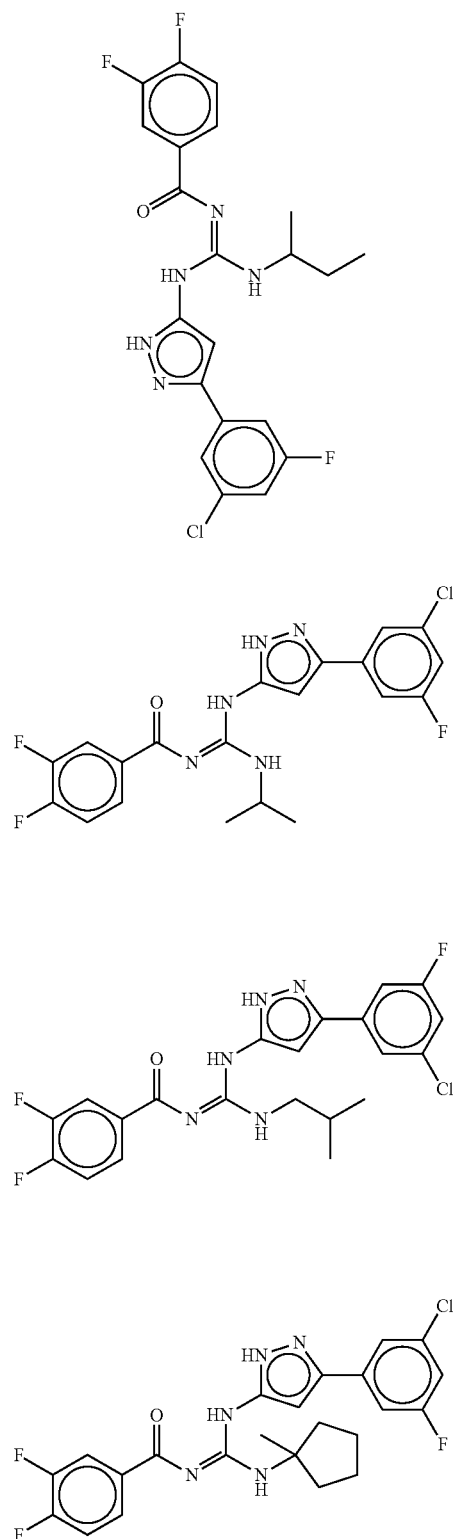
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A-288

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399

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Compound No.	Chemical Structure
A-289	
A-290	
A-291	
A-292	
A-293	

400

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Compound No.	Chemical Structure
A-294	
A-295	
A-296	

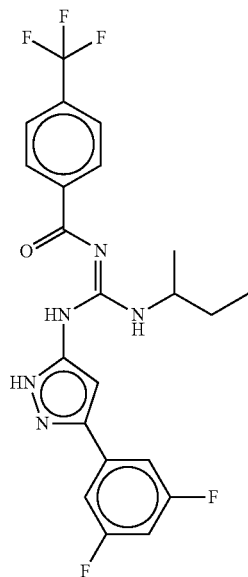
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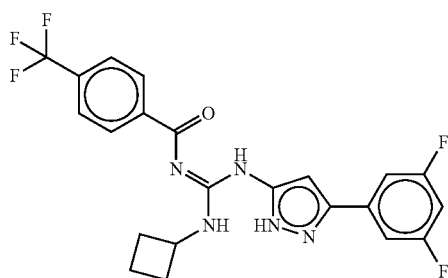
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Chemical Structure

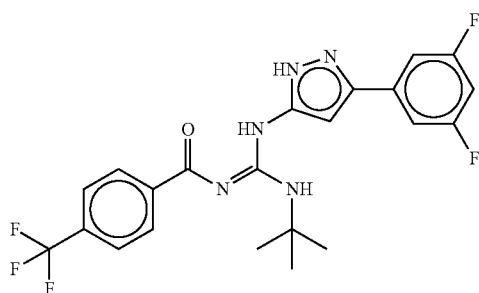
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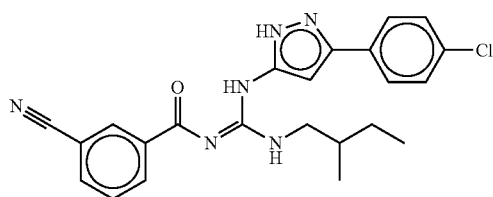
A-298



A-299



A-300



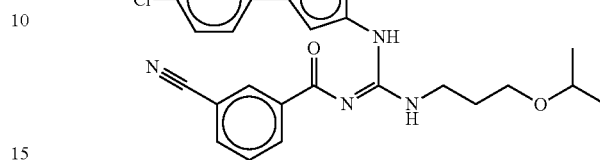
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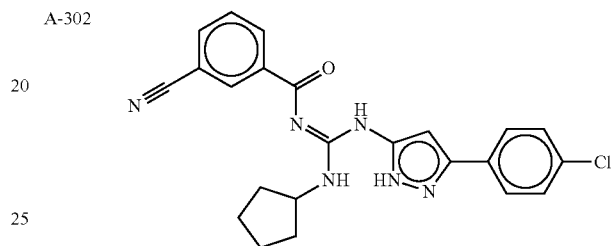
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Chemical Structure

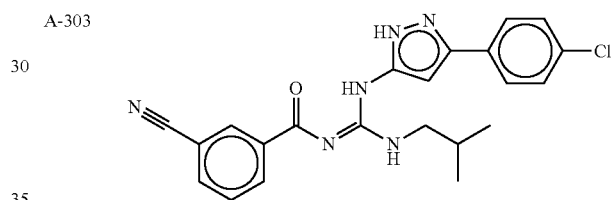
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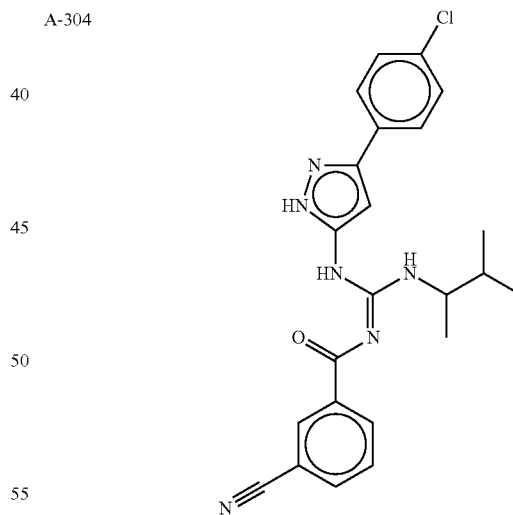
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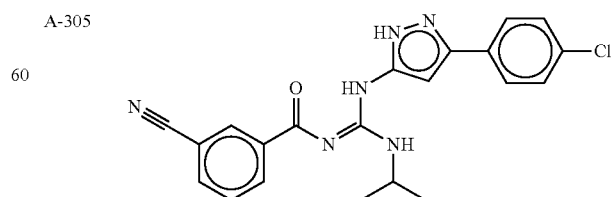
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A-304

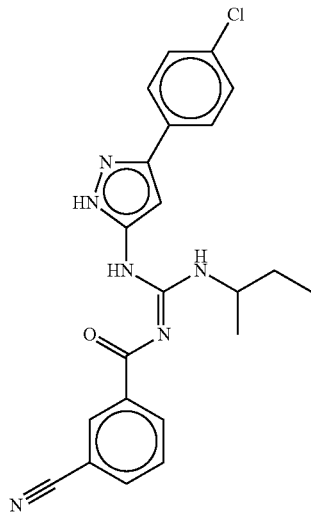
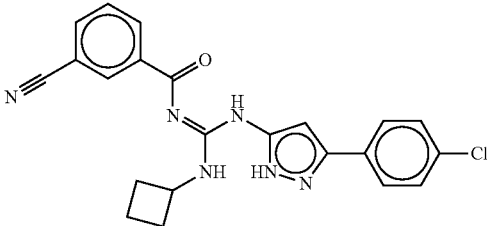
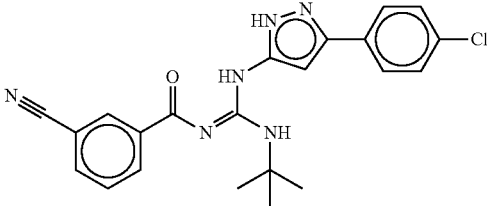
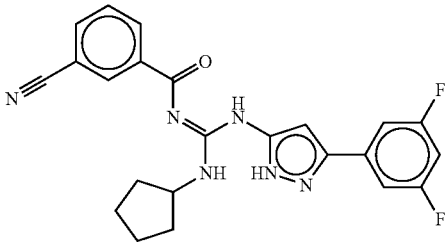
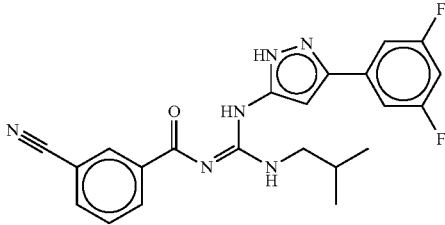


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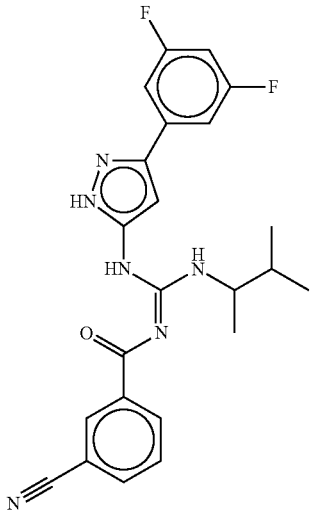
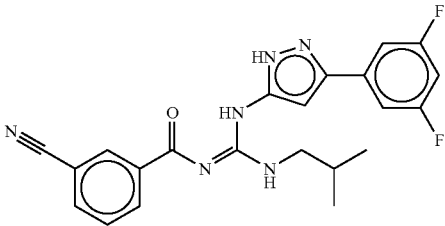
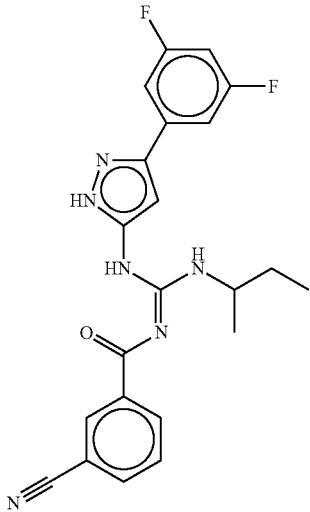
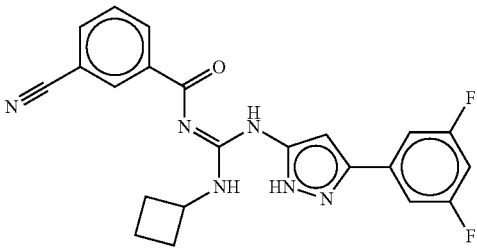
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Compound No.	Chemical Structure
A-306	
A-307	
A-308	
A-309	
A-310	

404

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Compound No.	Chemical Structure
A-311	
A-312	
A-313	
A-314	

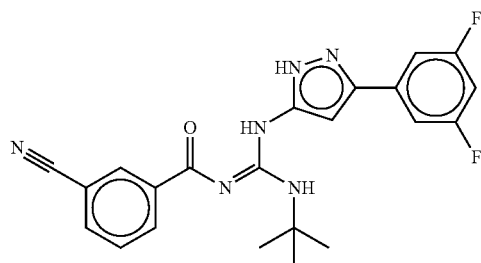
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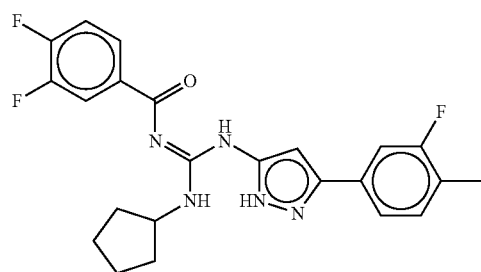
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No.

Chemical Structure

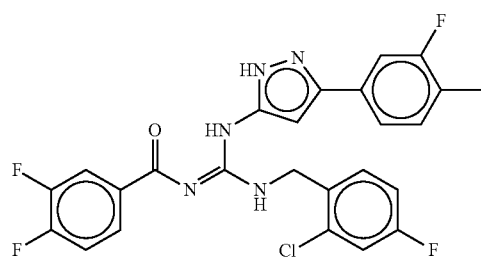
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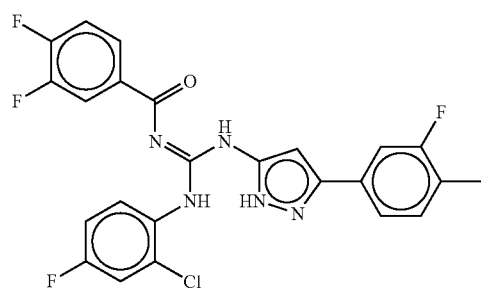
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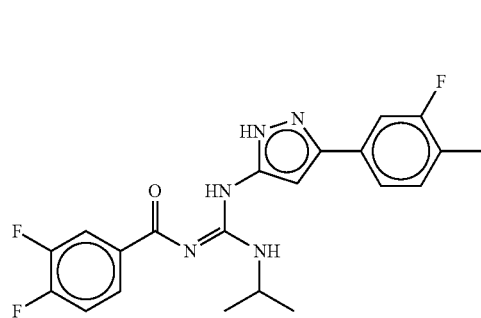
A-317



A-318



A-319



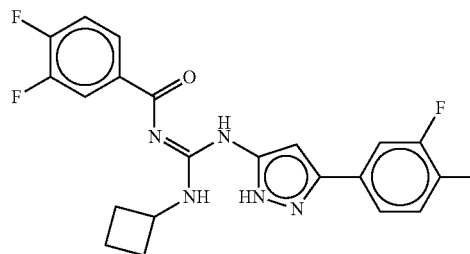
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Com-  
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No.

Chemical Structure

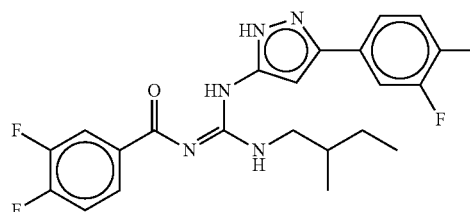
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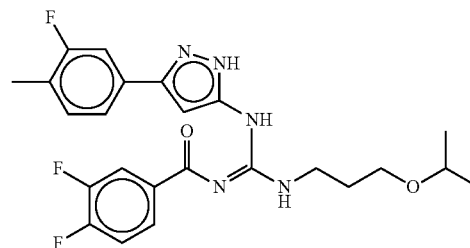
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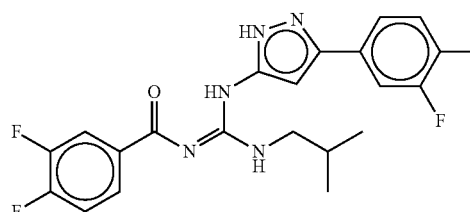
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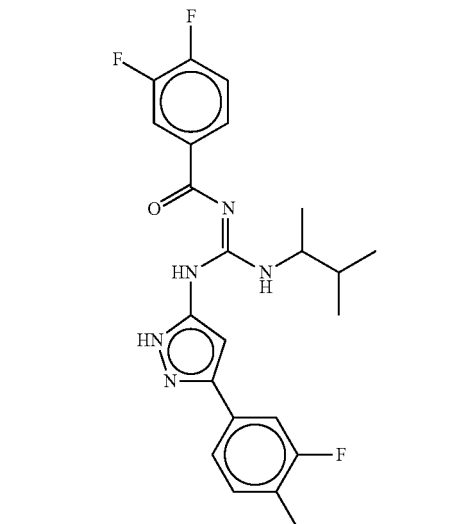
A-323



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A-324



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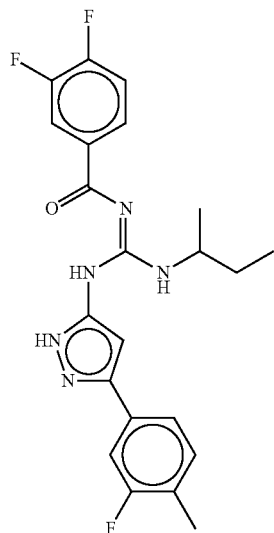
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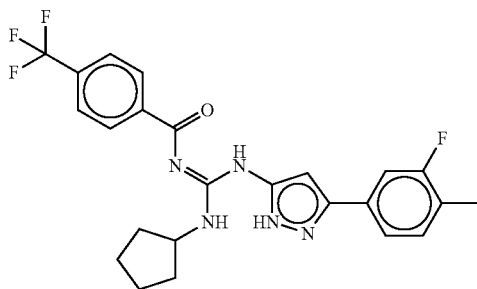
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Chemical Structure

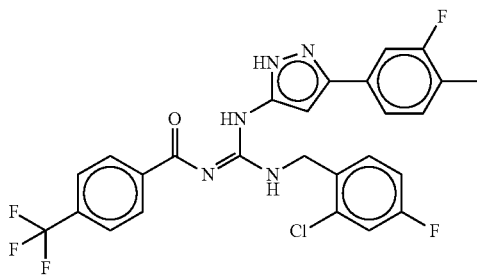
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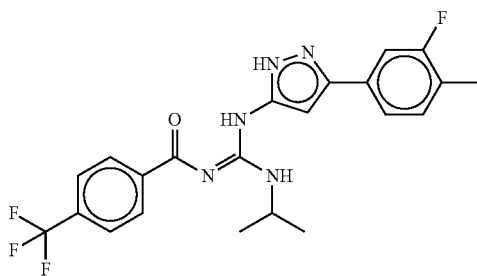
A-326



A-327



A-328

**408**

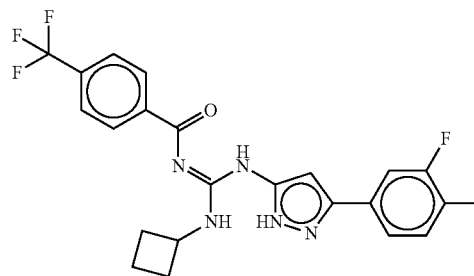
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No.

Chemical Structure

A-329

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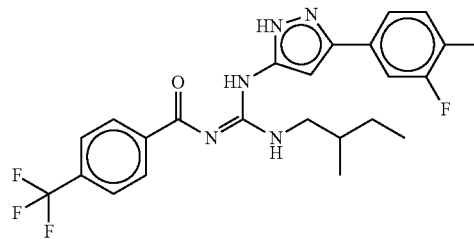
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A-330

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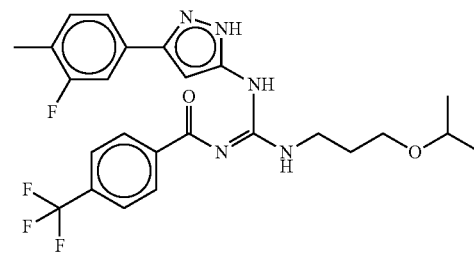
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A-331

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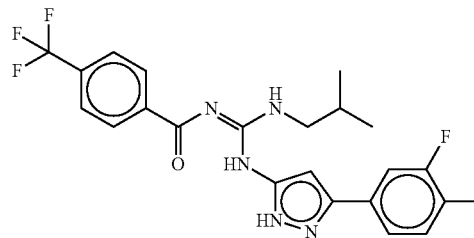


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A-332

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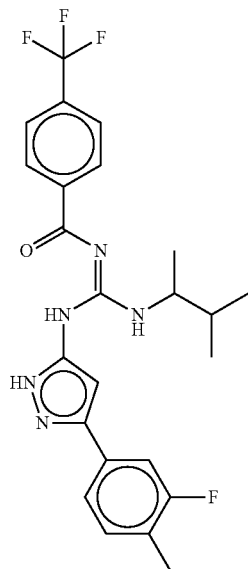
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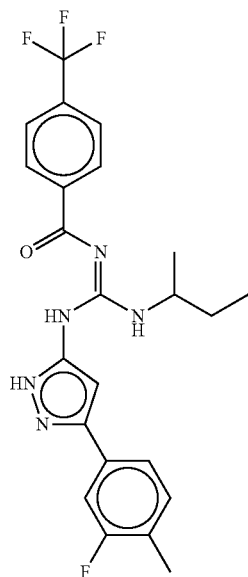
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Chemical Structure

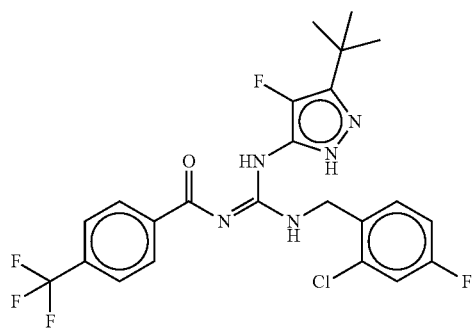
A-333



A-334



A-335



410

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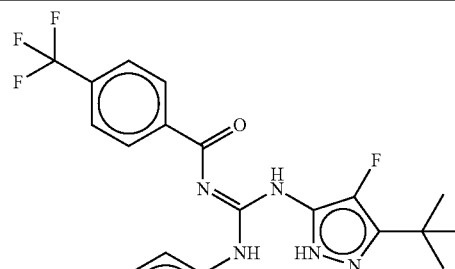
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Chemical Structure

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A-336

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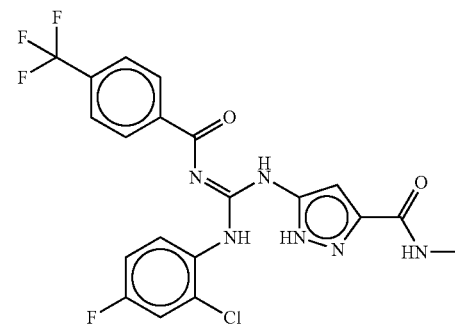
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A-337

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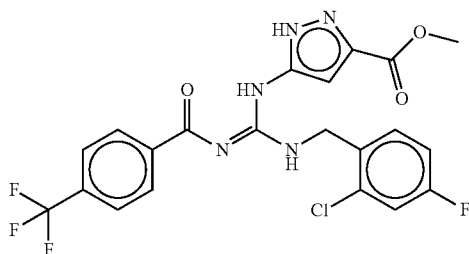
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A-338

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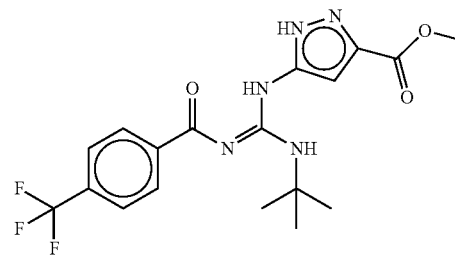
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A-339

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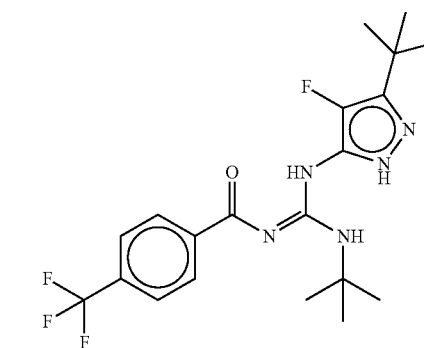


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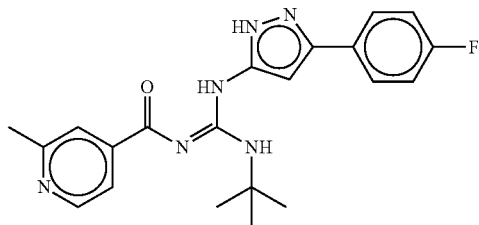
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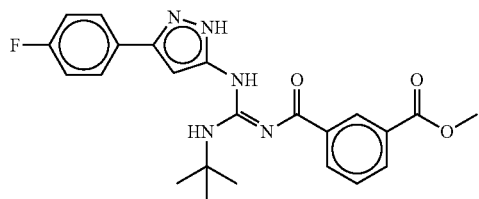
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No.

Chemical Structure

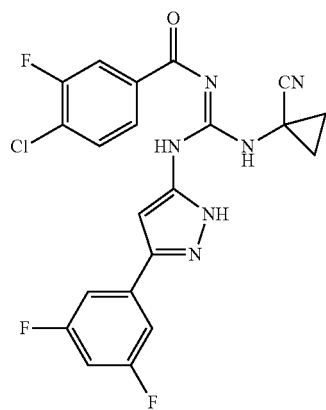
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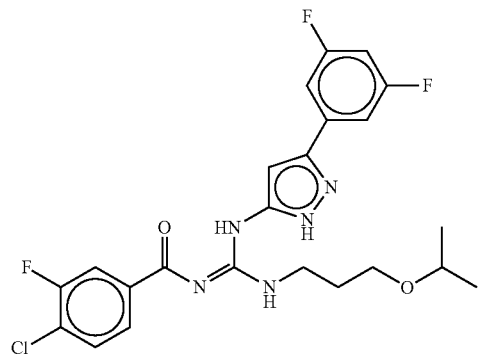
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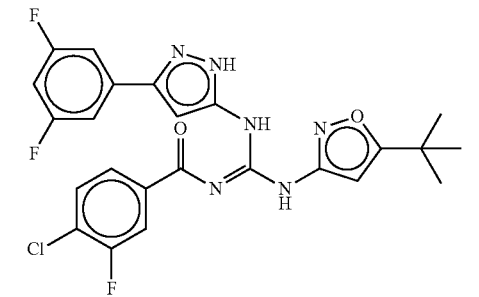
A-343



A-344



A-345



412

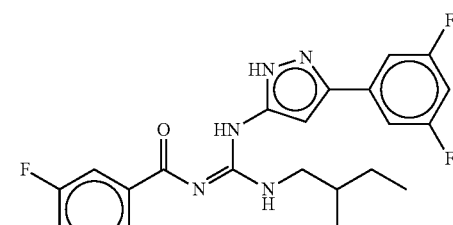
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Compound  
No.

Chemical Structure

A-346

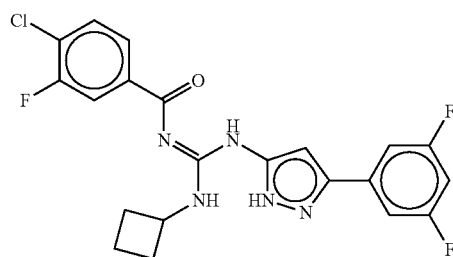
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A-347

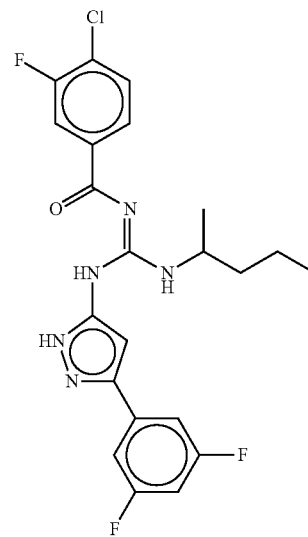
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A-348

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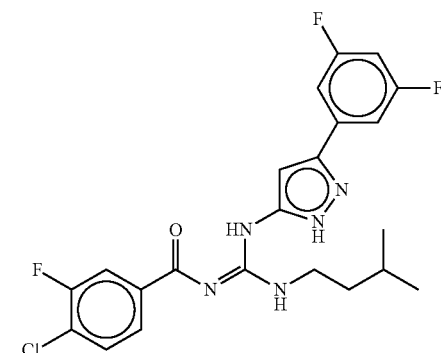
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A-349

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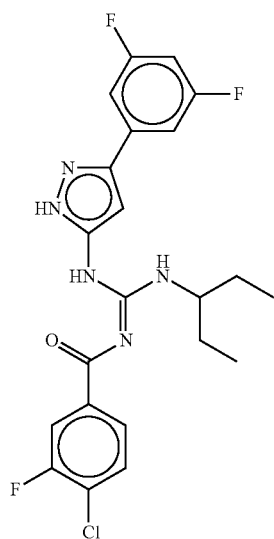
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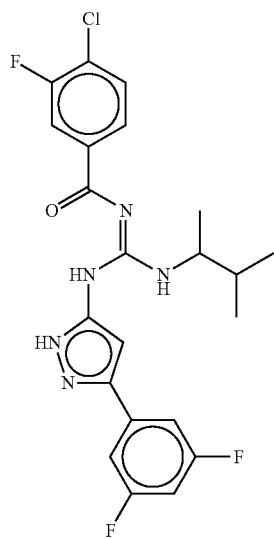
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Chemical Structure

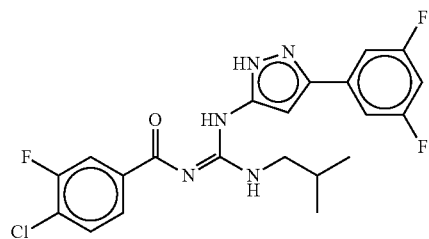
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A-351



A-352



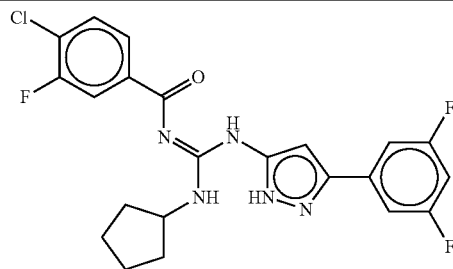
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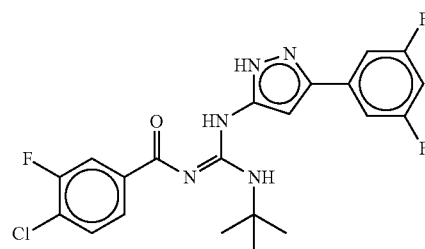
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No.

Chemical Structure

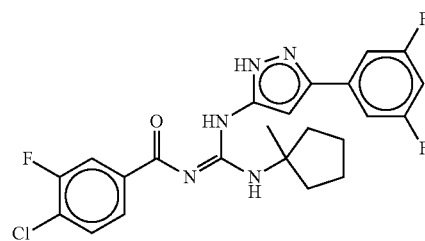
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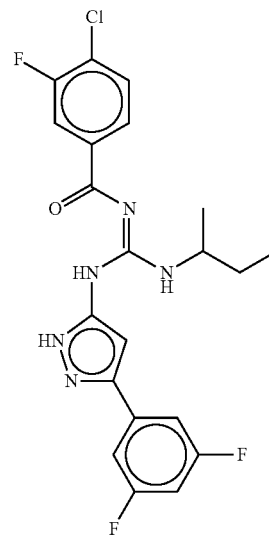
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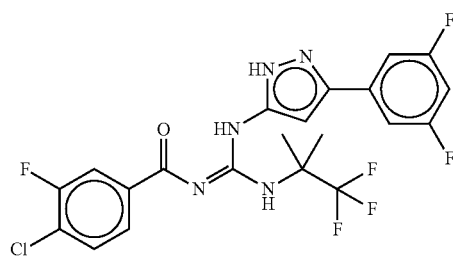
A-355



A-356



A-357



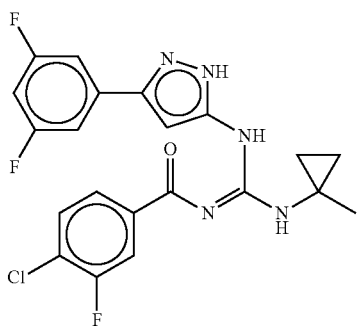
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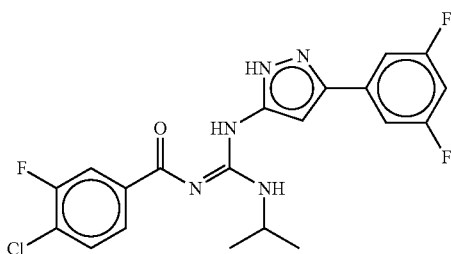
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Chemical Structure

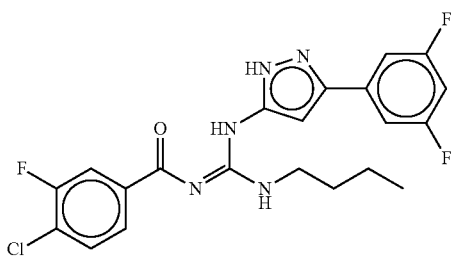
A-358



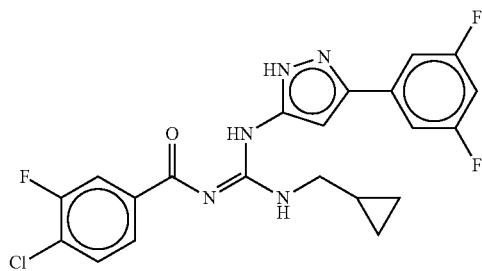
A-359



A-360



A-361



416

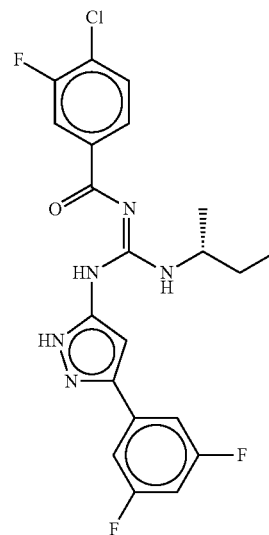
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No.

Chemical Structure

A-362

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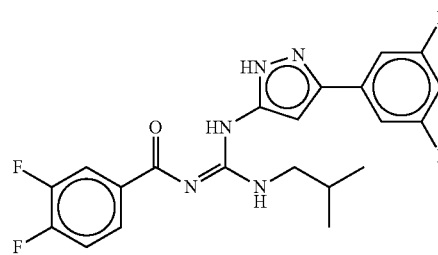
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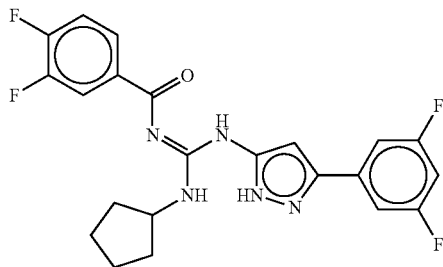
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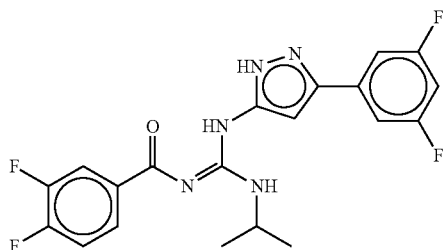
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Chemical Structure

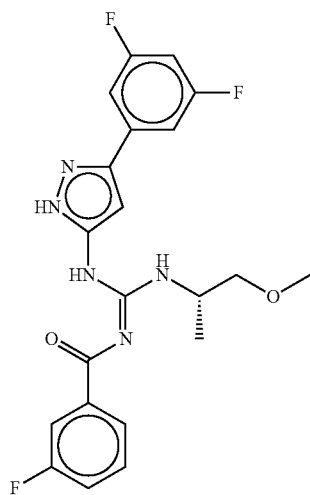
A-365



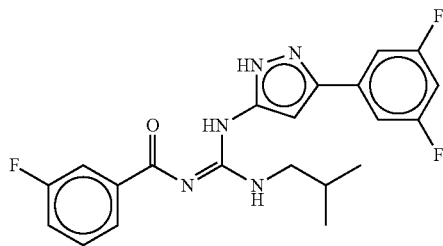
A-366



A-367



A-368



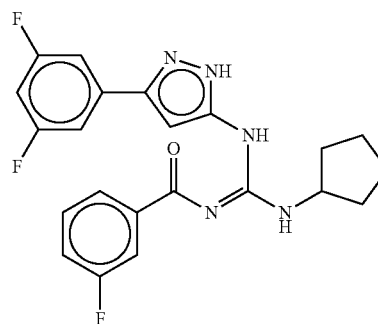
418

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Com-  
pound  
No.

Chemical Structure

A-369



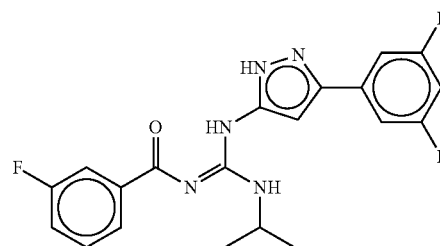
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A-370

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A-371

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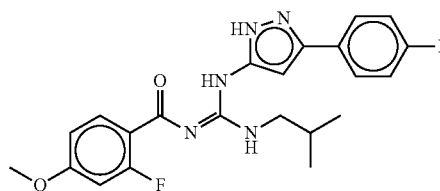
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A-372

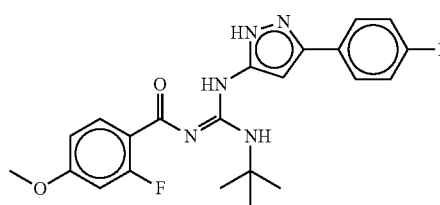
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A-373

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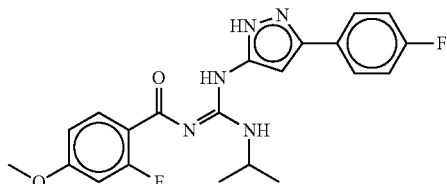
419

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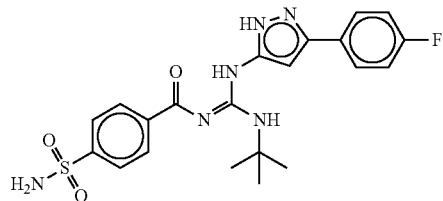
Com-  
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No.

Chemical Structure

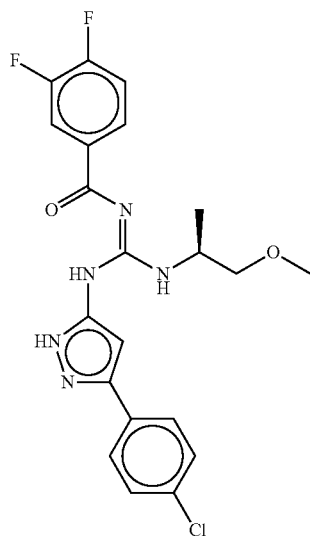
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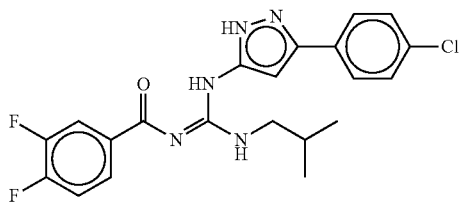
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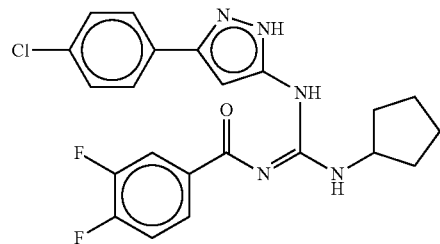
A-376



A-377



A-378



420

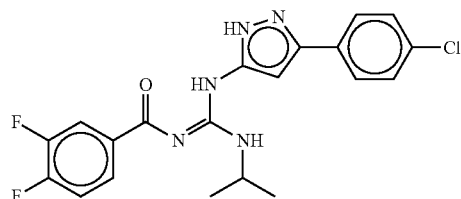
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Chemical Structure

A-379

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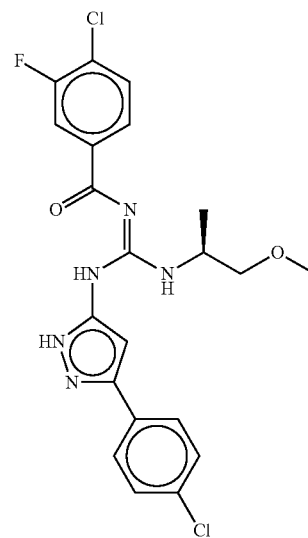
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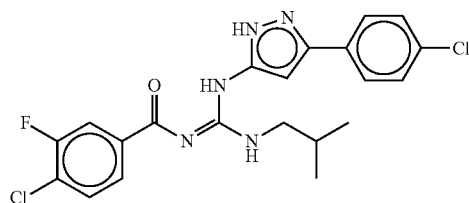
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A-381

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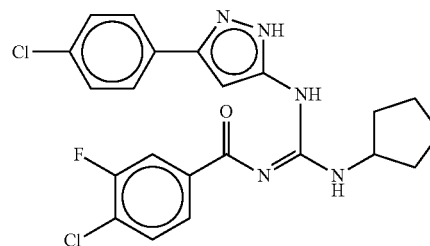
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A-382

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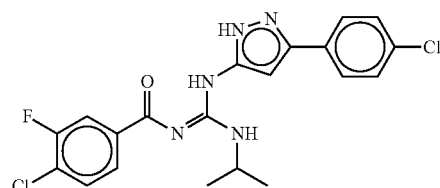
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A-383

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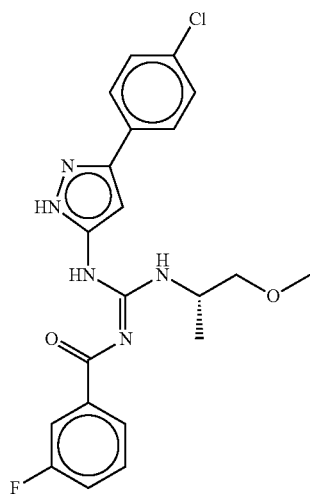
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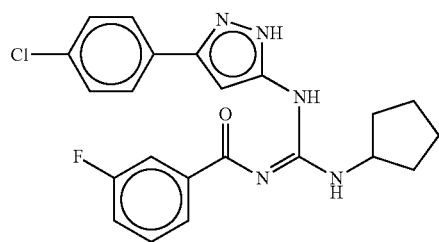
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Chemical Structure

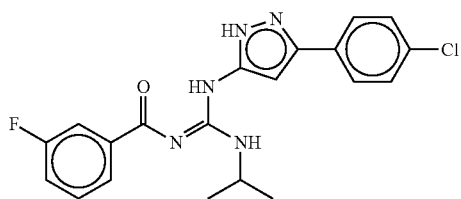
A-384



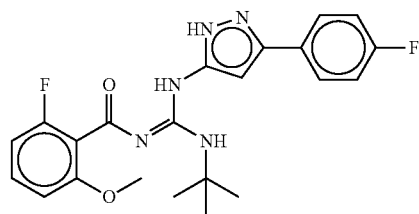
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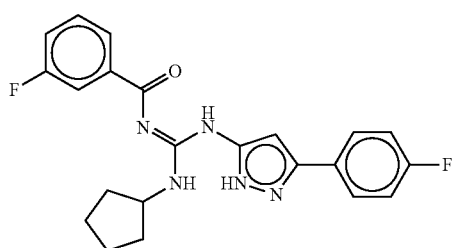
A-386



A-387



A-388



422

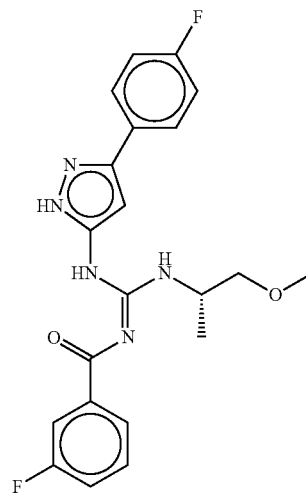
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Com-  
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No.

Chemical Structure

A-389

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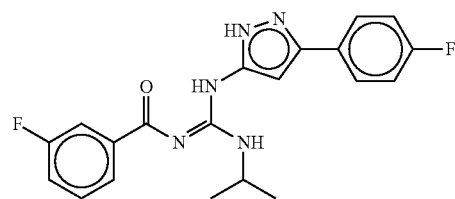
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A-390

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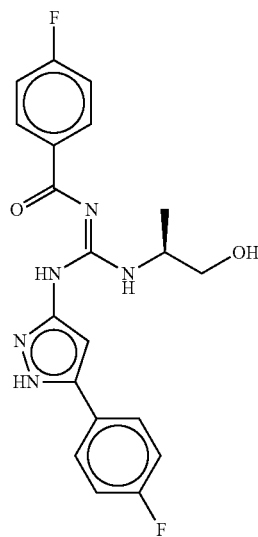


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A-391

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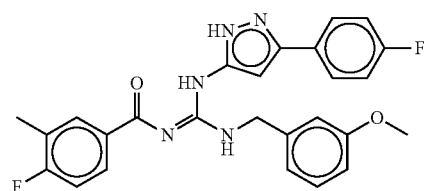


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A-392

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423

-continued

Compound No.	Chemical Structure
A-393	
A-394	
A-395	
A-396	
A-397	
A-398	
A-399	

424

-continued

Compound No.	Chemical Structure
A-400	
A-401	
A-402	
A-403	
A-404	

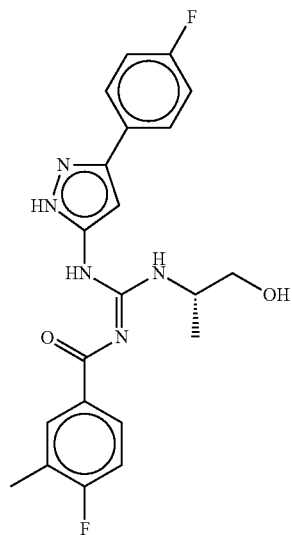
425

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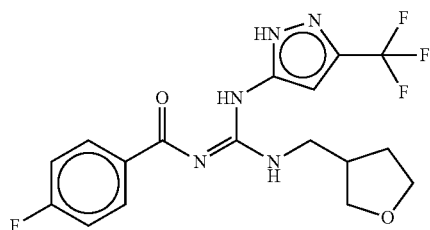
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Chemical Structure

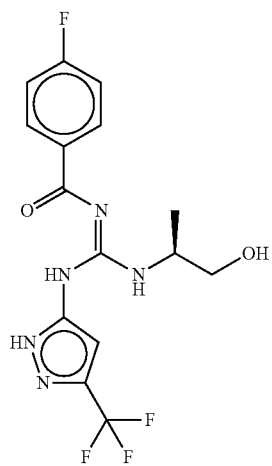
A-405



A-406



A-407



426

-continued

Com-  
pound  
No.

Chemical Structure

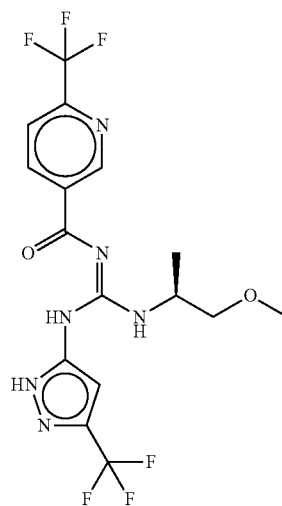
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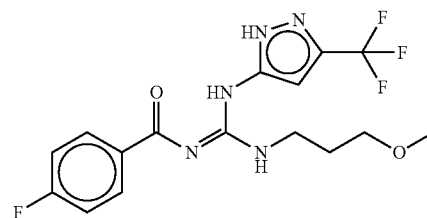
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A-409

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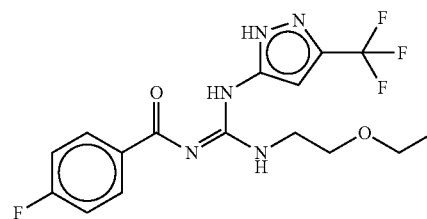
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A-410

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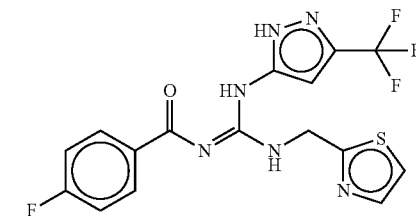
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A-411

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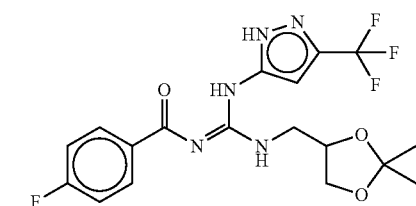
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A-412

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427

-continued

Compound No.	Chemical Structure
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A-414	
A-415	
A-416	
A-417	
A-418	

428

-continued

Compound No.	Chemical Structure
A-419	
A-420	
A-421	
A-422	
A-423	



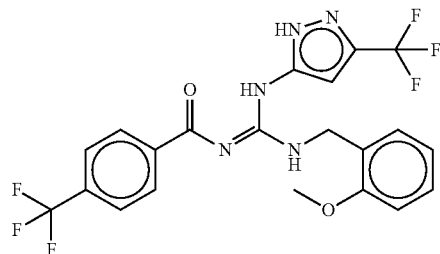
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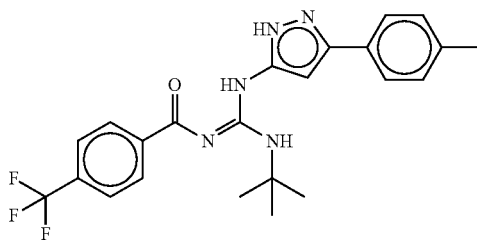
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Chemical Structure

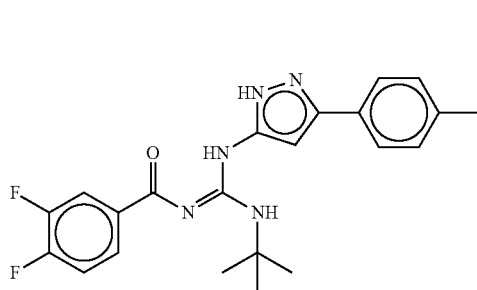
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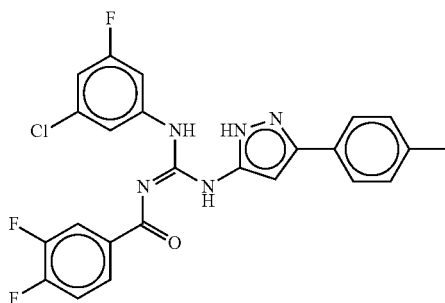
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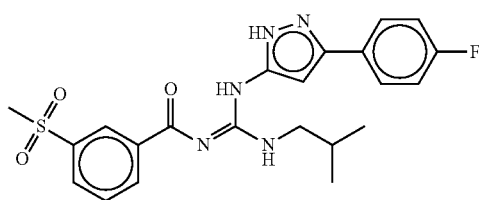
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A-428



A-429



430

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Com-  
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No.

Chemical Structure

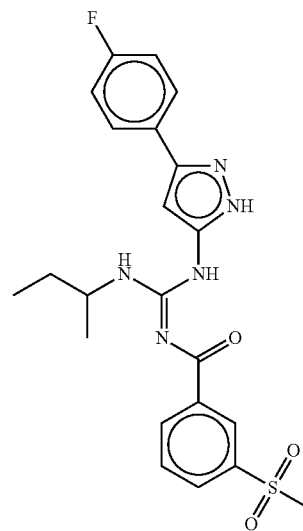
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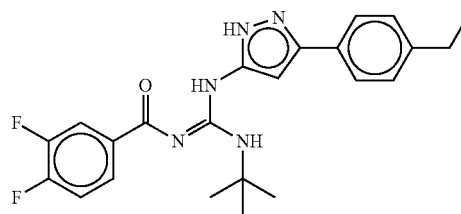
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A-431

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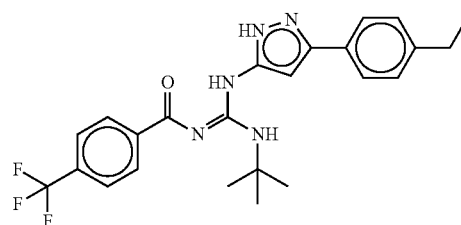
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A-432

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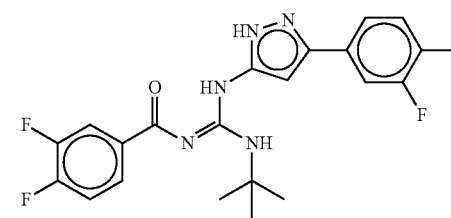
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A-433

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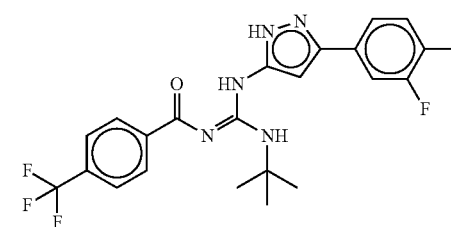
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A-434

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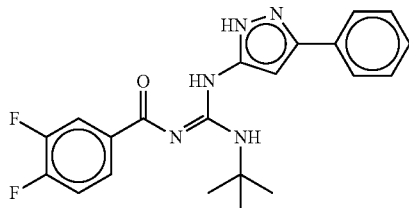
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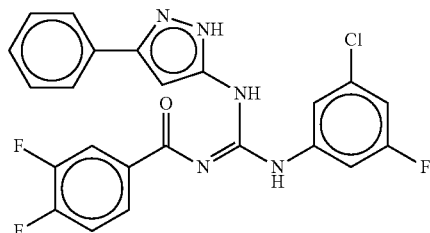
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Chemical Structure

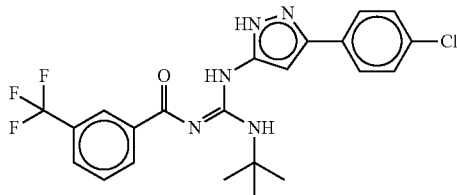
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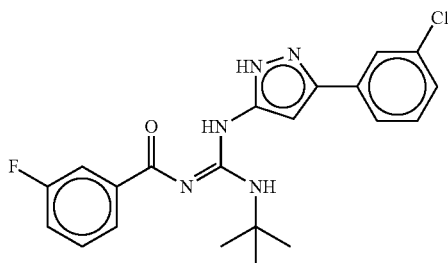
A-436



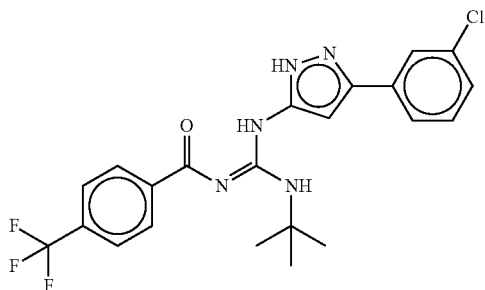
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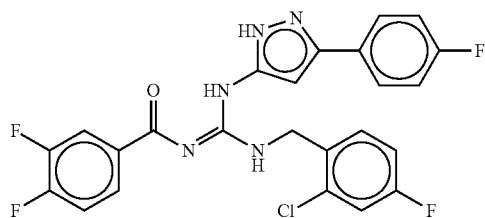
A-438



A-439



A-440



432

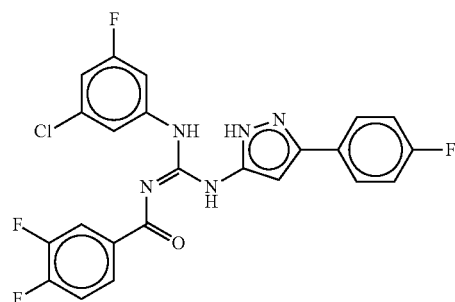
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No.

Chemical Structure

A-441

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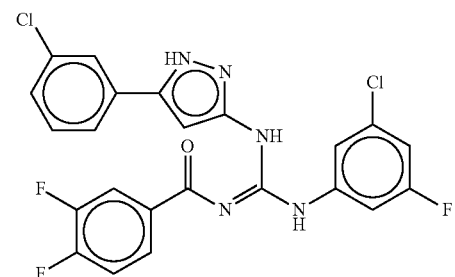
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A-442

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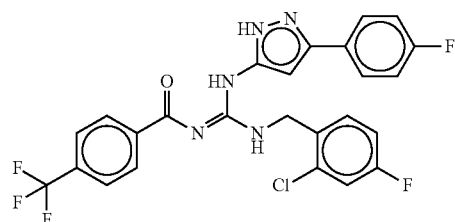
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A-443

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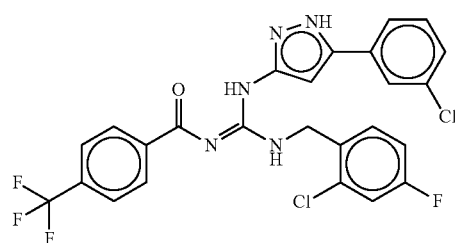
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A-444

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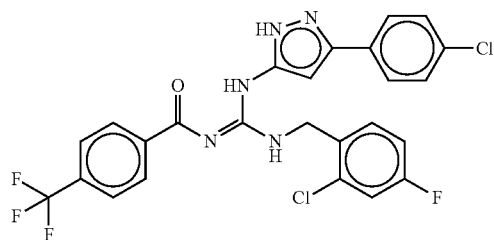


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A-445

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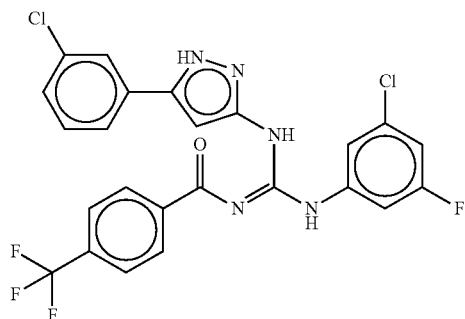
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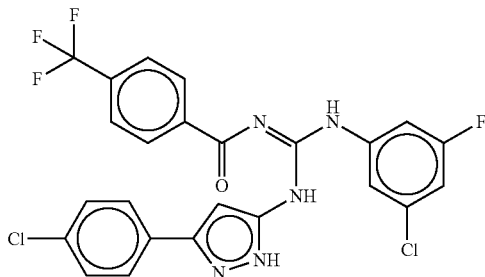
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Chemical Structure

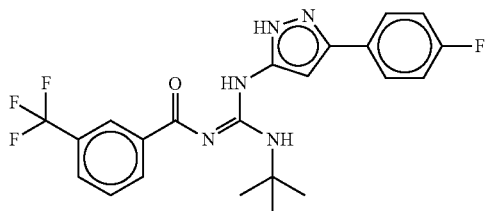
A-446



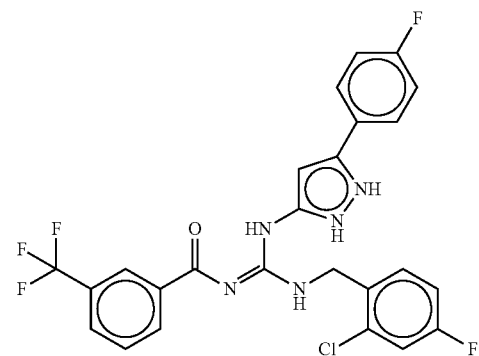
A-447



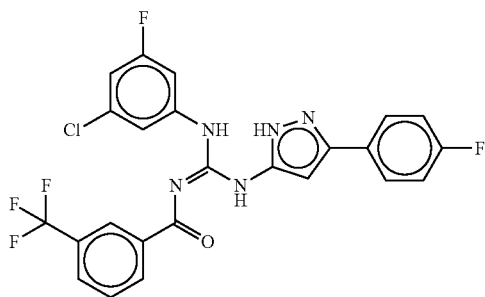
A-448



A-449



A-450



434

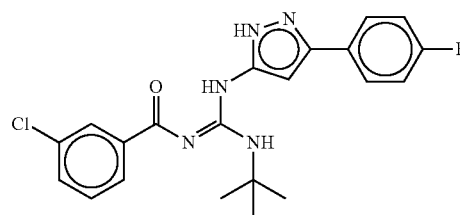
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Com-  
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Chemical Structure

A-451

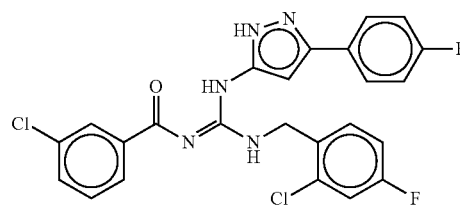
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A-452

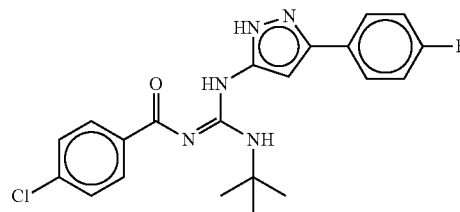
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A-453

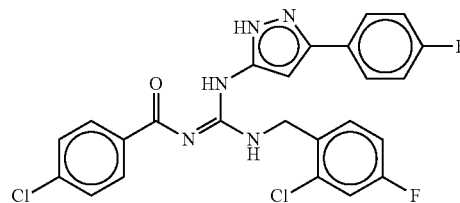
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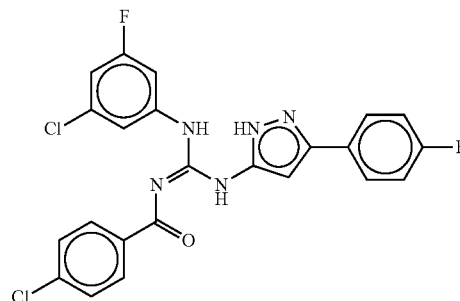
A-454

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45 A-455

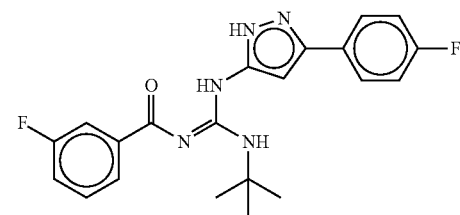
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A-456

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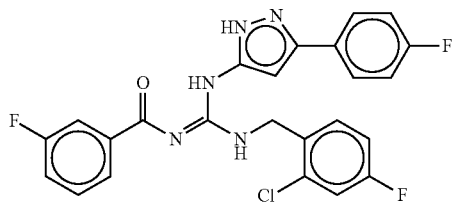
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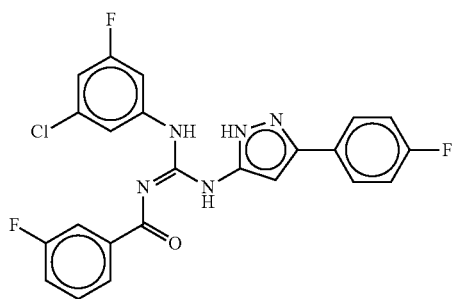
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Chemical Structure

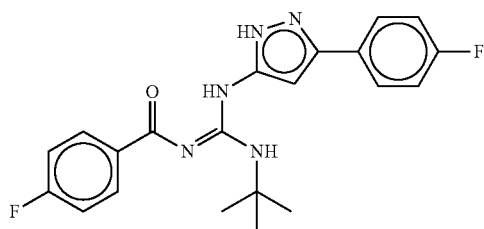
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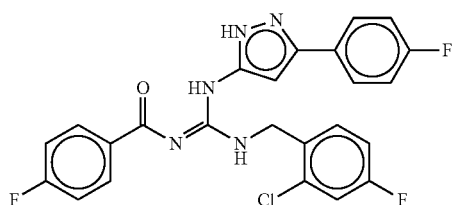
A-458



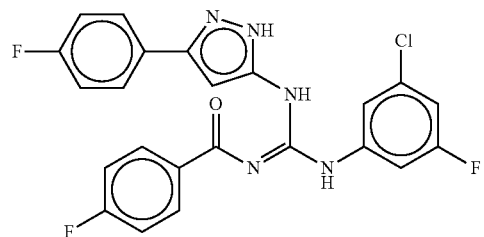
A-459



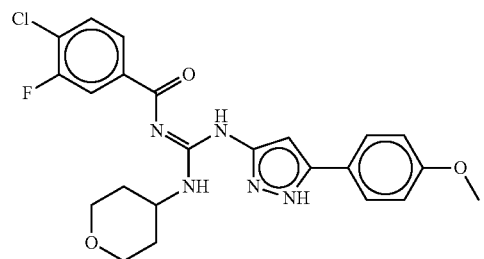
A-460



A-461



A-462



436

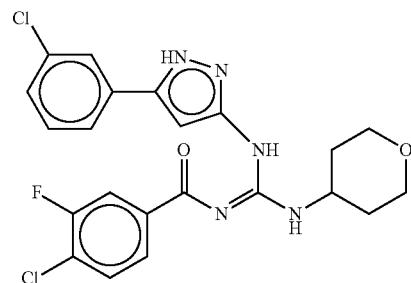
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Com-  
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No.

Chemical Structure

A-463

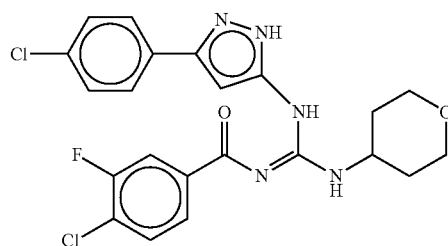
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A-464

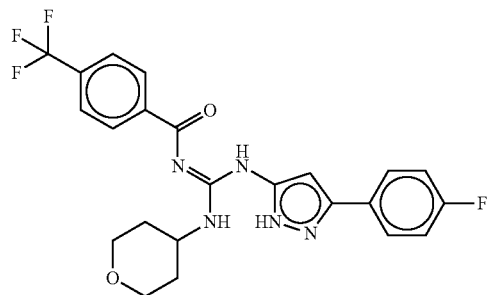
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A-465

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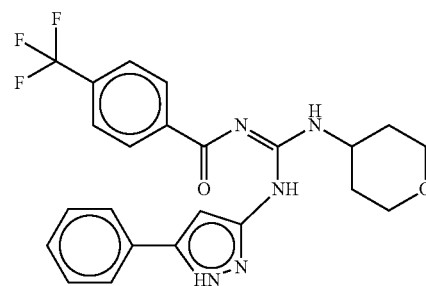


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A-466

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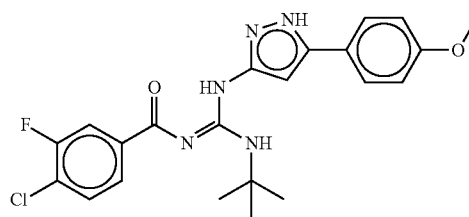


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A-467

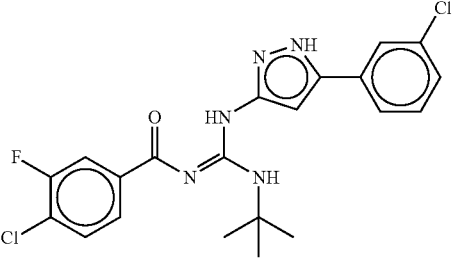
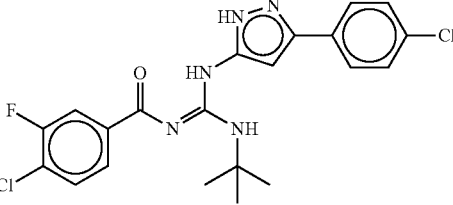
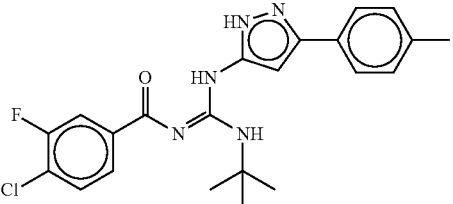
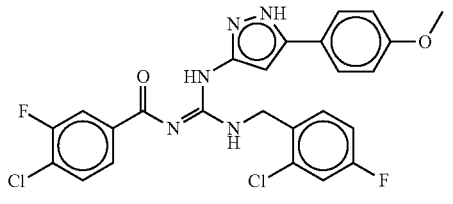
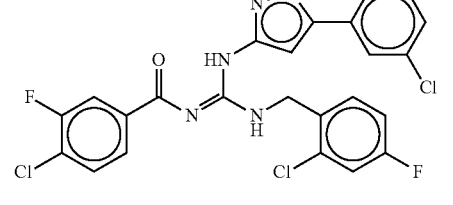
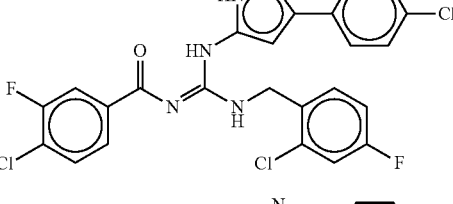
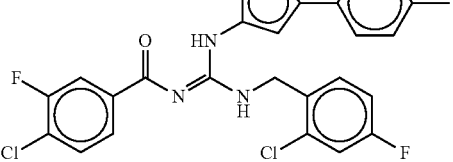
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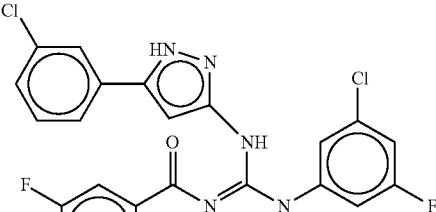
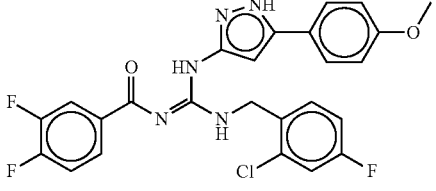
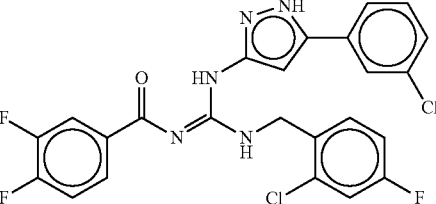
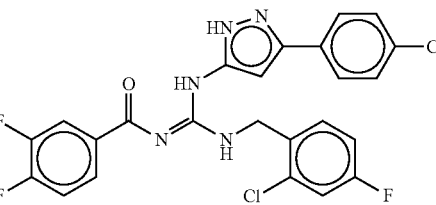
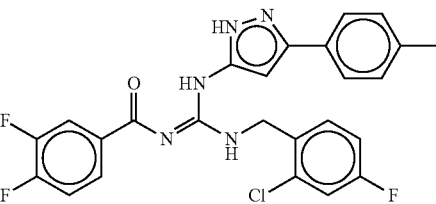
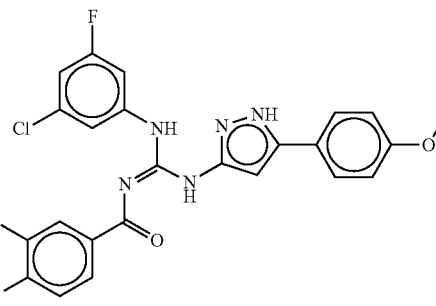
437

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Compound No.	Chemical Structure
A-468	
A-469	
A-470	
A-471	
A-472	
A-473	
A-474	

438

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Compound No.	Chemical Structure
A-475	
A-476	
A-477	
A-478	
A-479	
A-480	

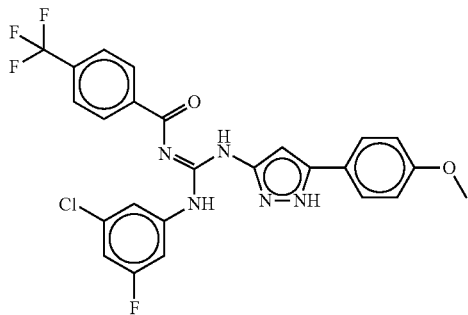
439

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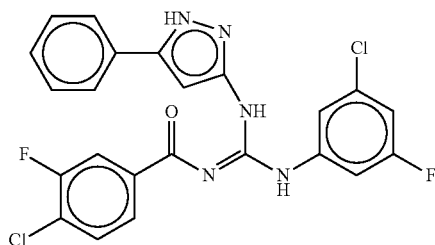
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No.

Chemical Structure

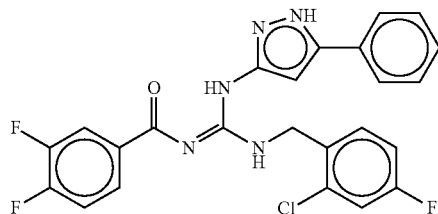
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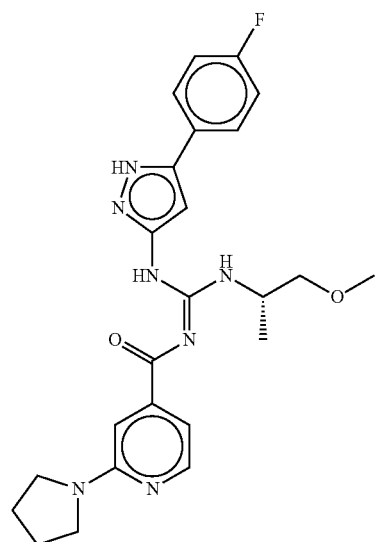
A-482



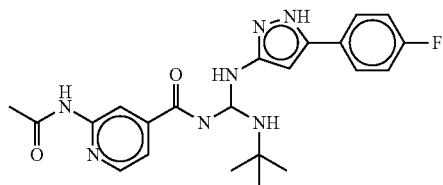
A-483



A-484



A-485



440

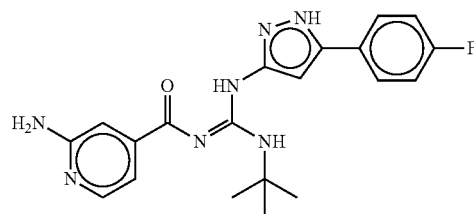
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Compound  
No.

Chemical Structure

A-486

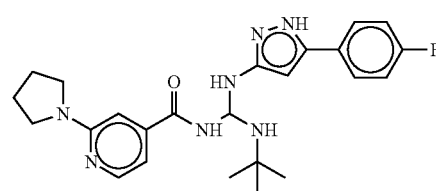
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A-487

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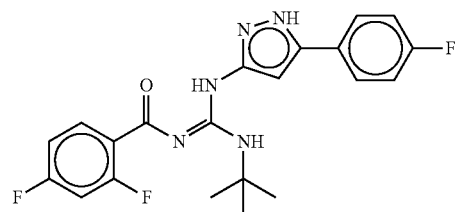
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A-489

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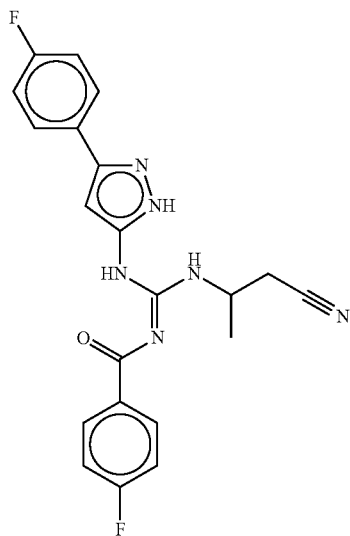
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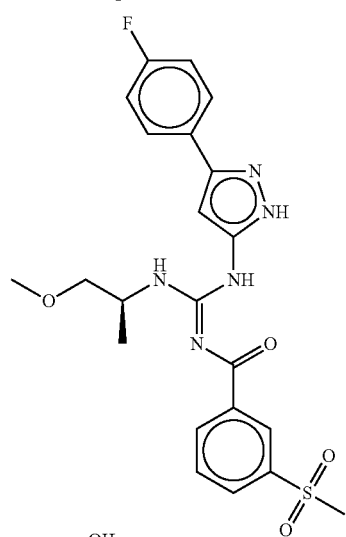
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Chemical Structure

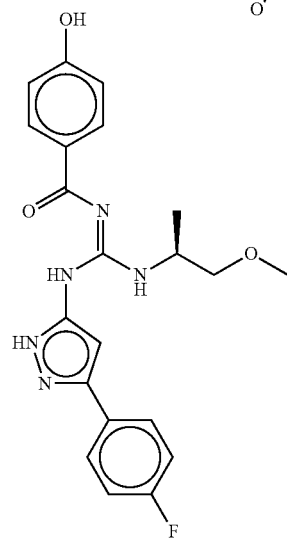
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A-491



A-492



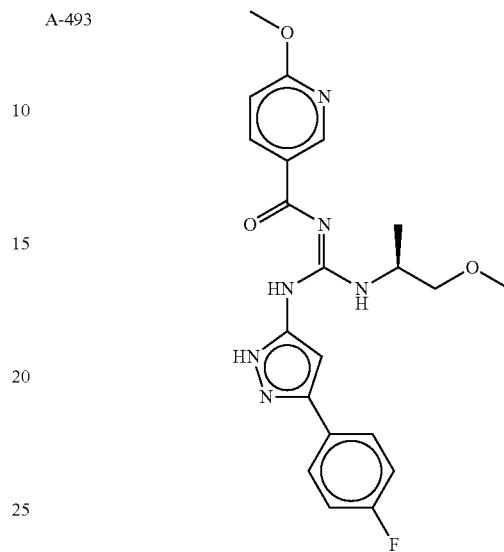
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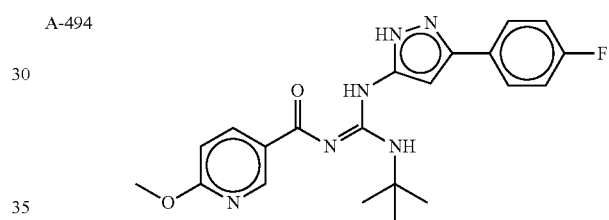
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Chemical Structure

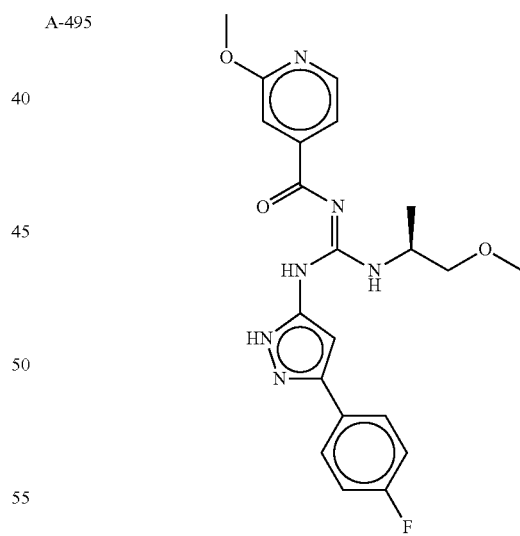
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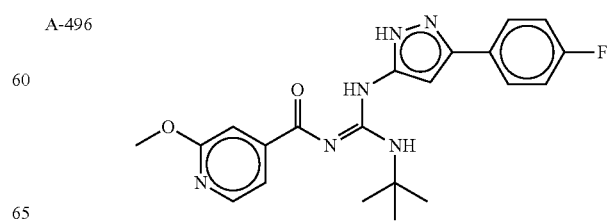
A-494



A-495



A-496



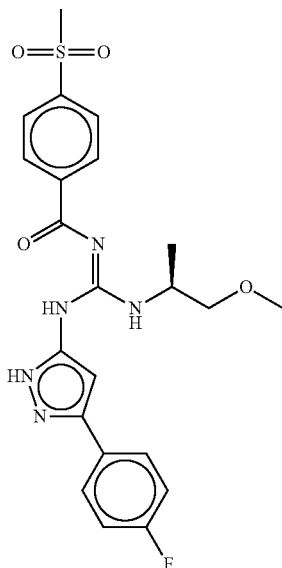
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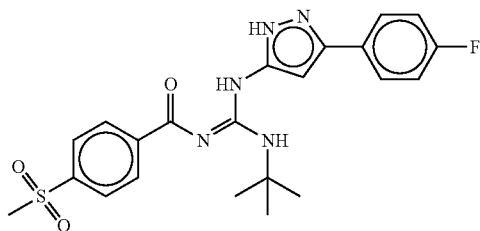
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Chemical Structure

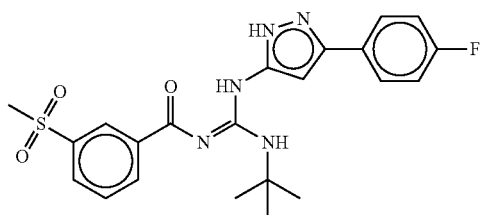
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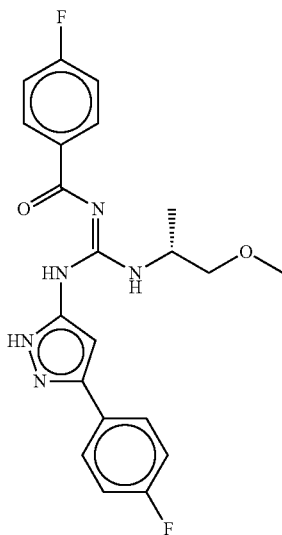
A-498



A-499



A-500



444

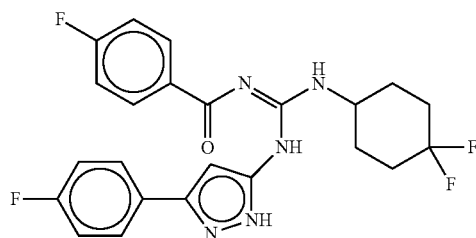
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Compound  
No.

Chemical Structure

A-501

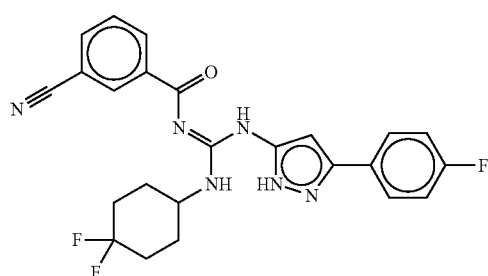
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A-502

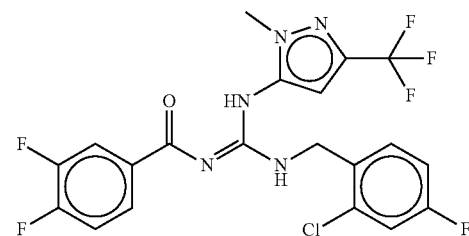
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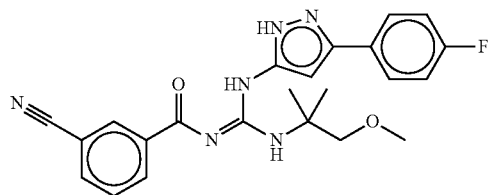
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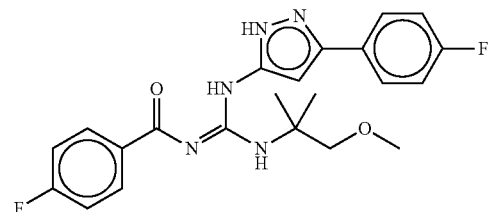
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A-505

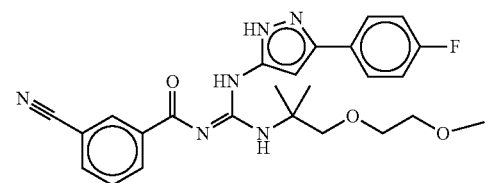
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A-506

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Compound No.	Chemical Structure
A-507	
A-508	
A-509	
A-510	
A-511	
A-512	
A-513	

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Compound No.	Chemical Structure
A-514	
A-515	
A-516	
A-517	
A-518	
A-519	

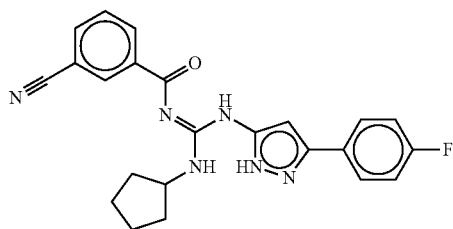
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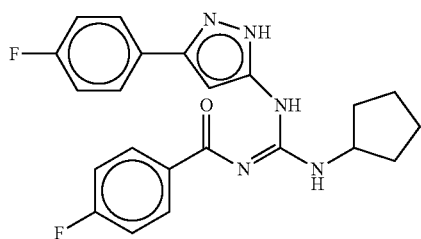
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No.

Chemical Structure

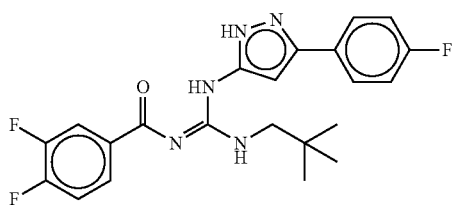
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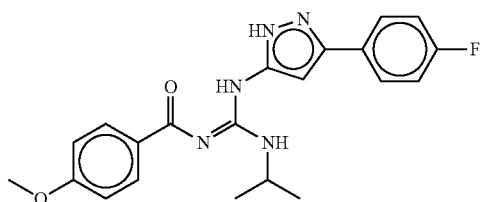
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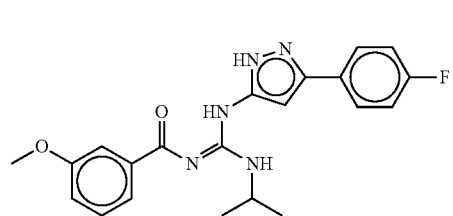
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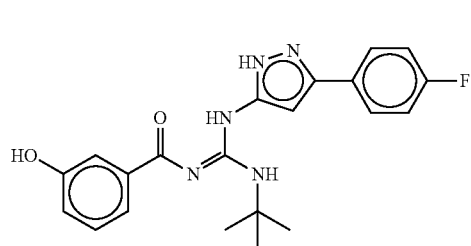
A-523



A-524



A-525



448

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Com-  
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No.

Chemical Structure

A-526

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A-527

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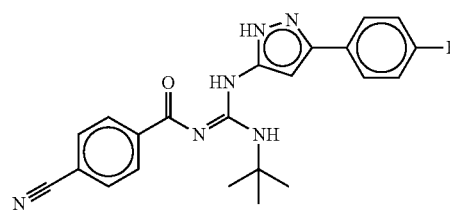
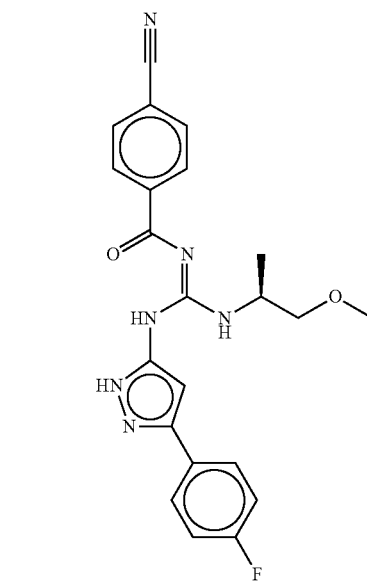
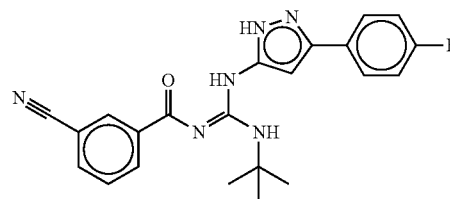
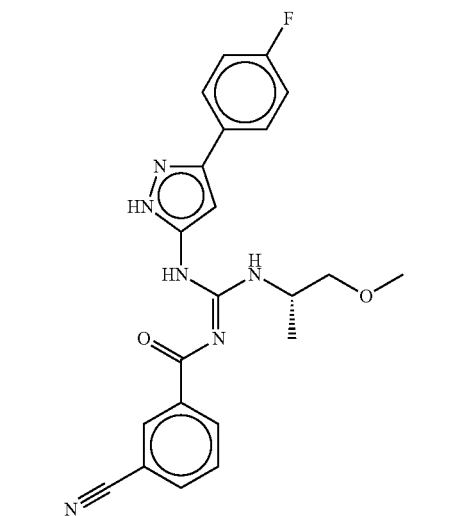
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A-529

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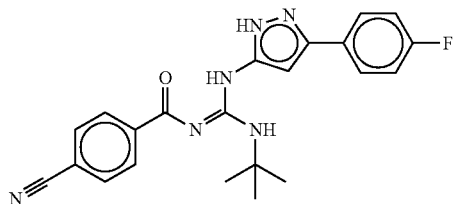
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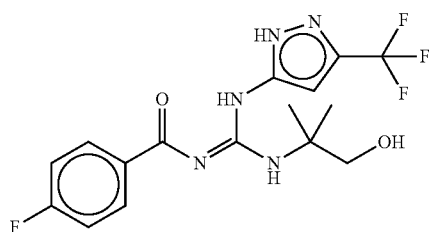
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Chemical Structure

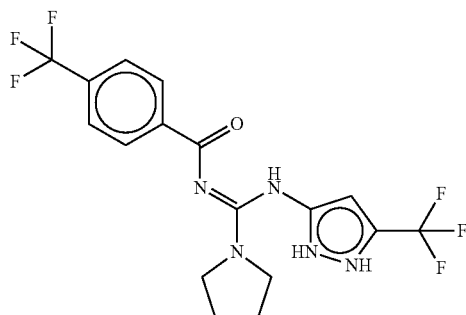
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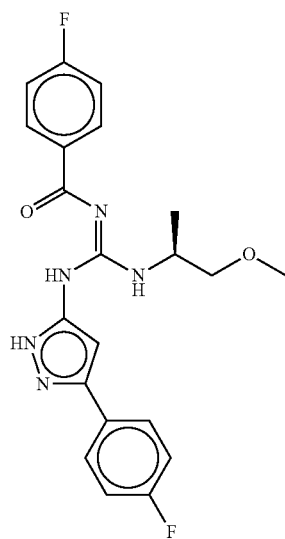
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A-532



A-533



450

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No.

Chemical Structure

A-534

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A-535

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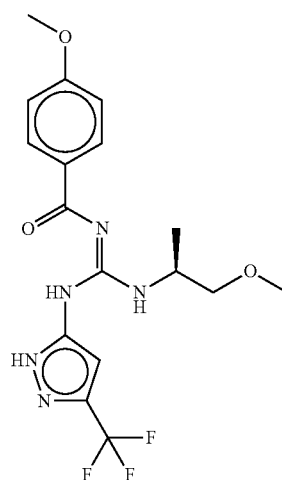
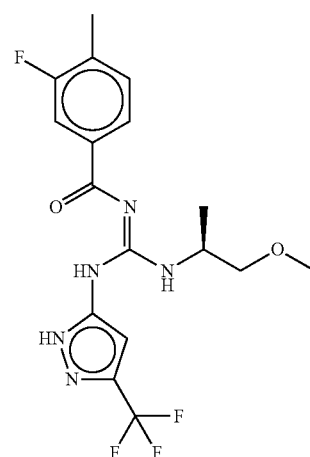
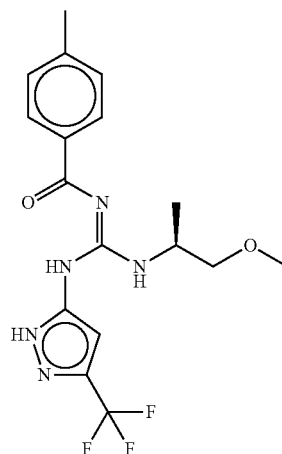
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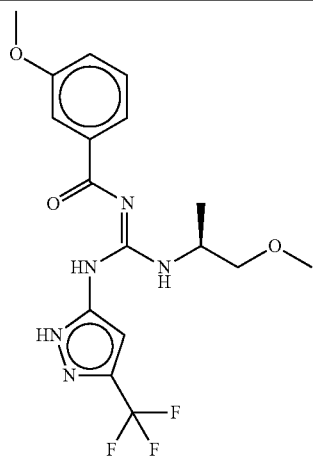
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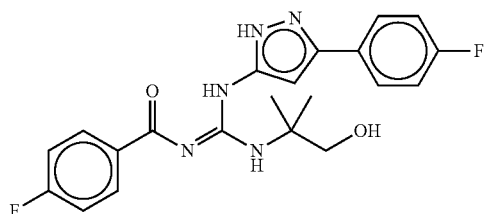
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Chemical Structure

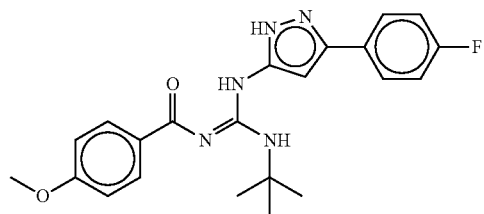
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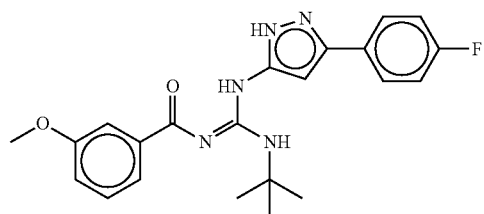
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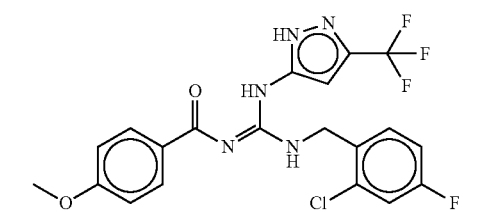
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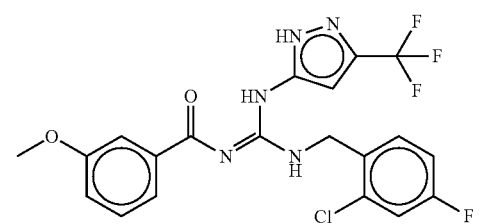
A-540



A-541



A-542



452

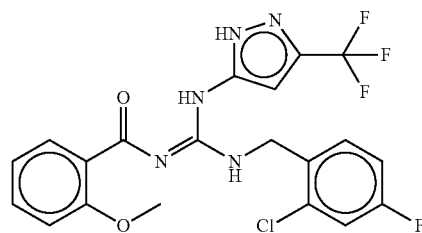
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Compound  
No.

Chemical Structure

A-543

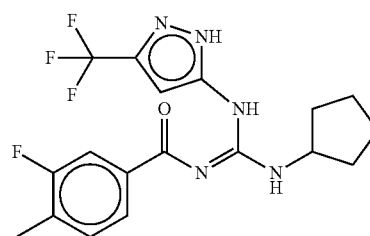
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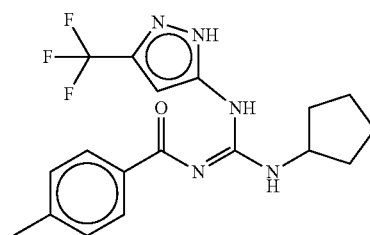
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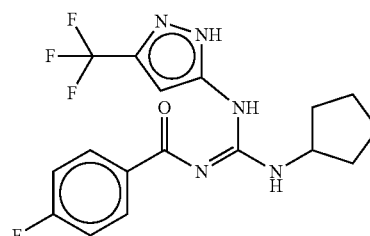
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A-548

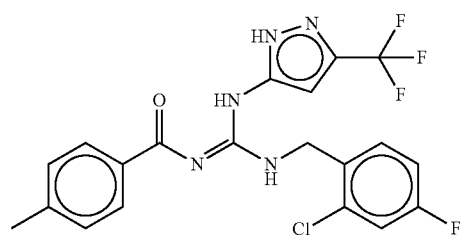
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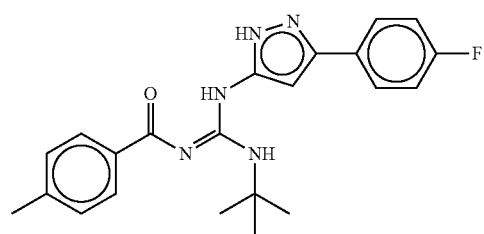
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A-550

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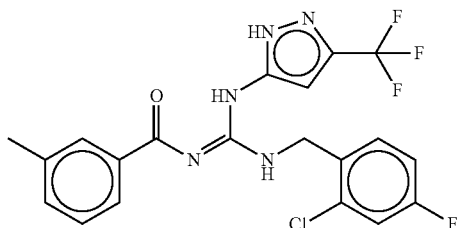
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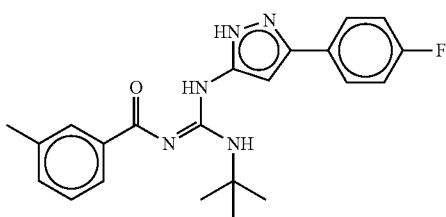
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Chemical Structure

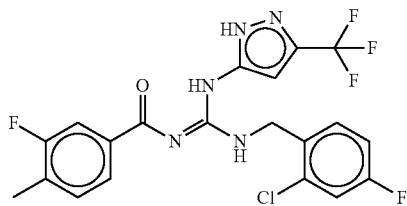
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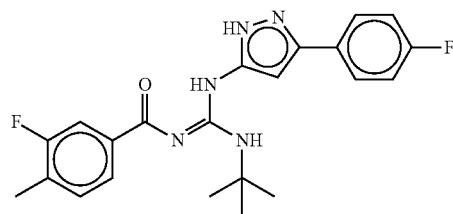
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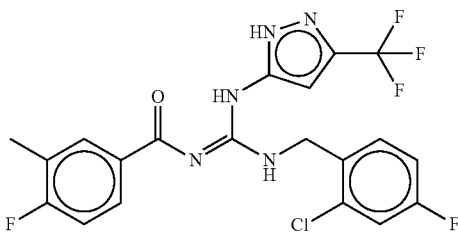
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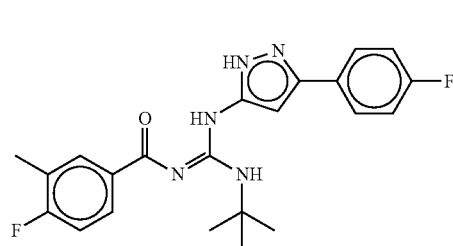
A-554



A-555



A-556



454

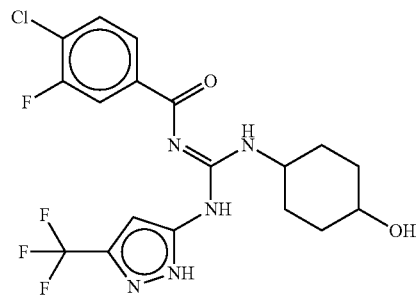
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Chemical Structure

A-557

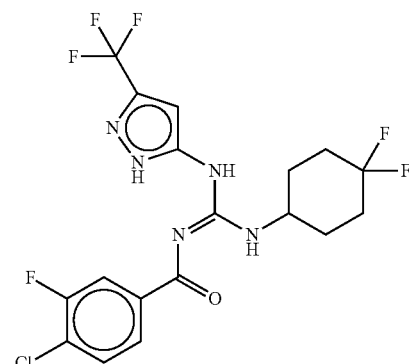
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A-558

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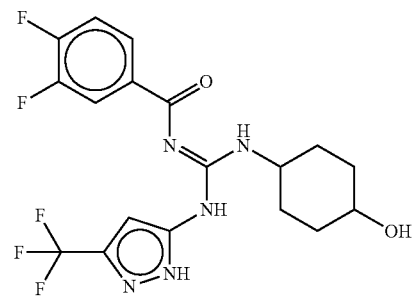


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A-559

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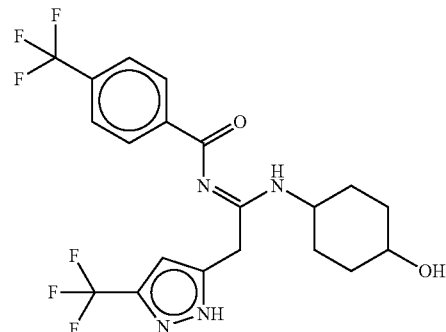


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A-560

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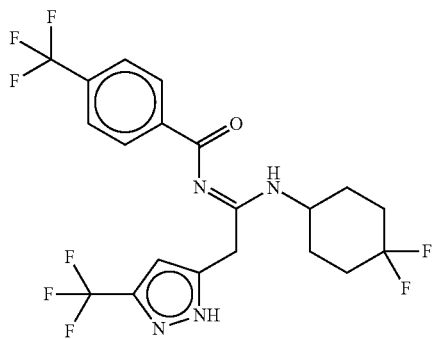
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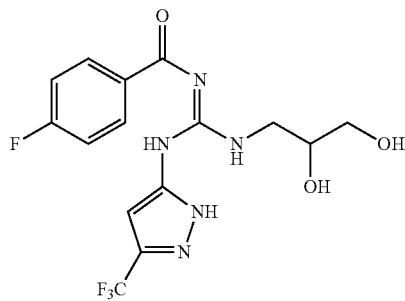
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Chemical Structure

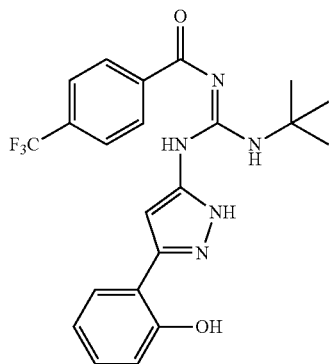
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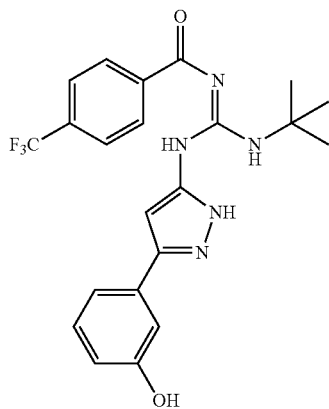
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A-563



A-564



456

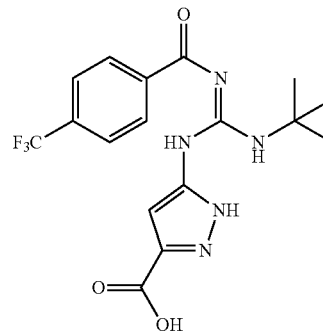
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No.

Chemical Structure

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A-567

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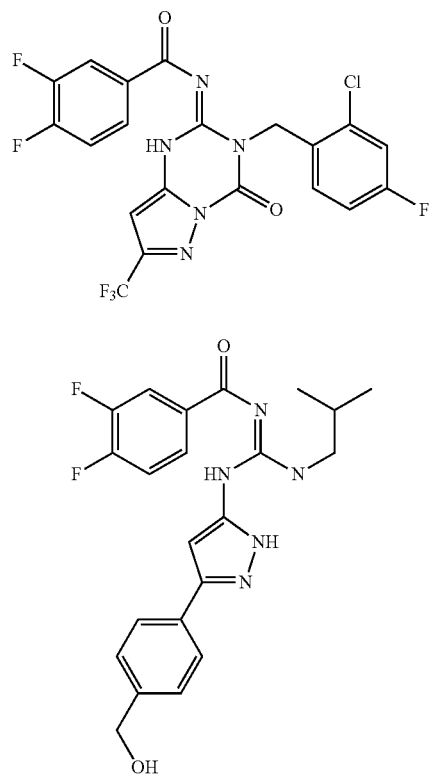
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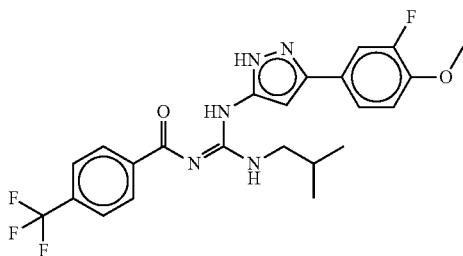
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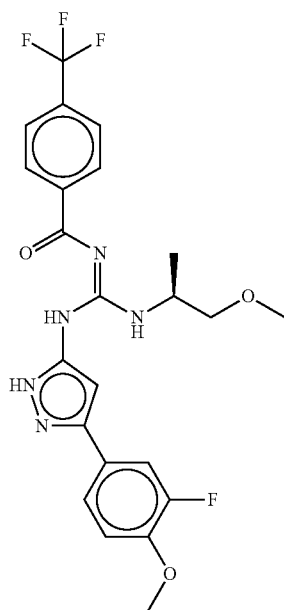
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Chemical Structure

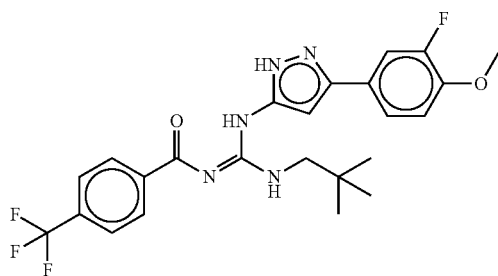
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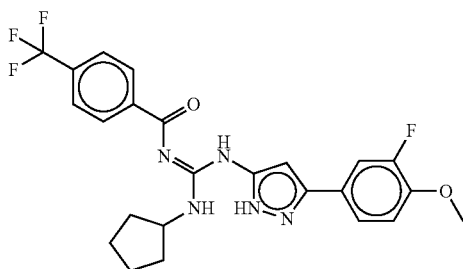
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A-573



A-574

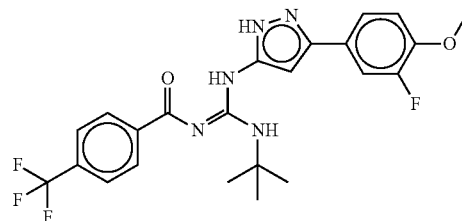
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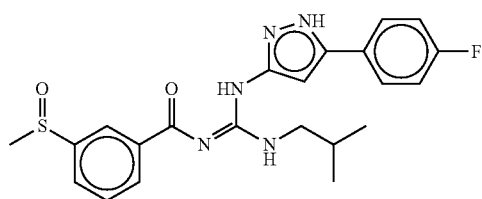
Chemical Structure

A-575



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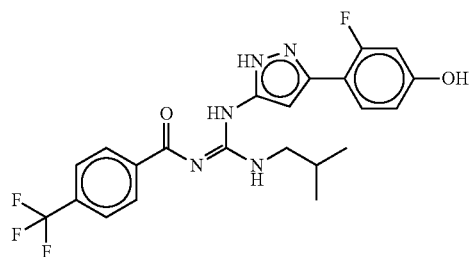
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A-577

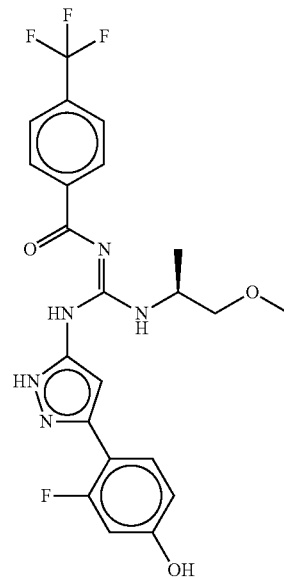
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A-578

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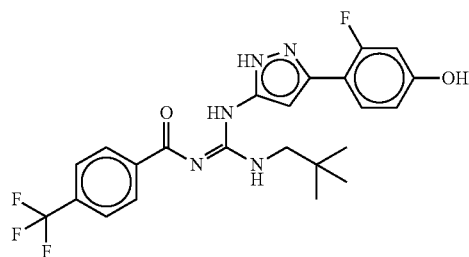
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A-579

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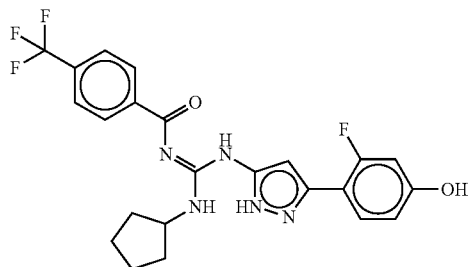
459

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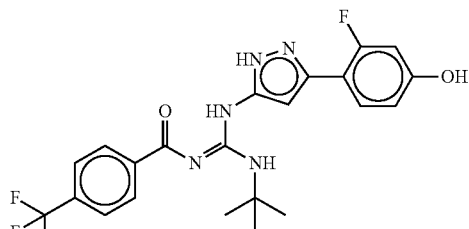
Com-  
pound  
No.

Chemical Structure

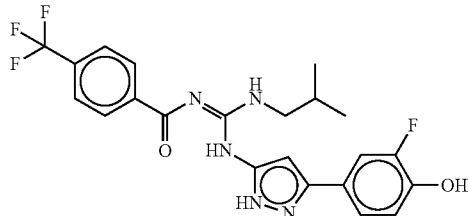
A-580



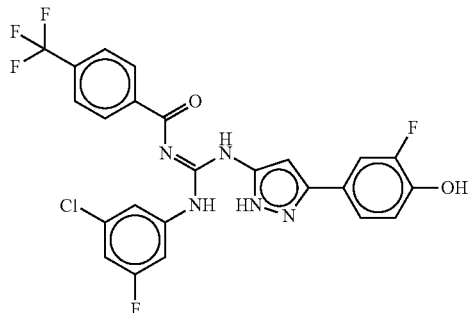
A-581



A-582



A-583



460

-continued

Com-  
pound  
No.

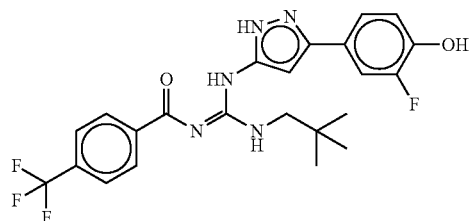
Chemical Structure

5

A-584

10

15

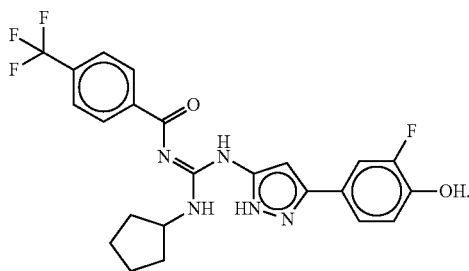


A-585

20

25

30

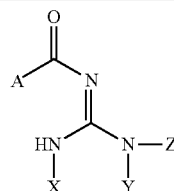


26. A pharmaceutical composition comprising a compound of claim 1 and a pharmaceutically acceptable carrier.

27. A method of treating a disorder selected from the group consisting of an immune disorder, inflammatory disorder, cardiovascular disease, myeloma, lymphoma, cancer, and bacterial infection, comprising administering to a patient in need thereof a therapeutically effective amount of a compound of claim 1 in order to ameliorate a symptom of the disorder.

28. A method of inhibiting a  $F_1F_0$ -ATPase, comprising exposing a  $F_1F_0$ -ATPase to a compound claim of 1 to inhibit said  $F_1F_0$ -ATPase.

29. The compound of claim 1, wherein the compound is one of the following or a pharmaceutically acceptable salt thereof:



No.

A

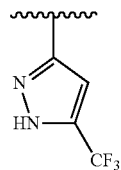
X

Y

Z

I-1

3-chlorophenyl

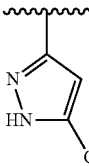
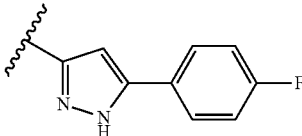
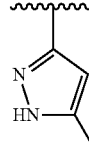
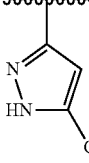
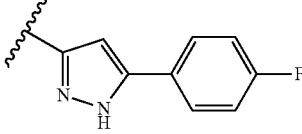
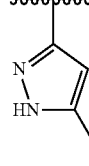
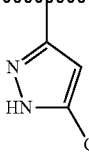
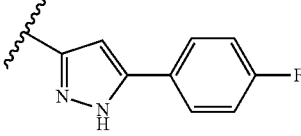


H

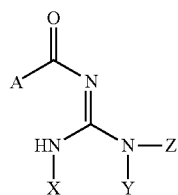
3-chlorophenyl



$$\begin{array}{c} \text{O} \\ \parallel \\ \text{A} - \text{C} - \text{N} \\ \parallel \\ \text{HN} - \text{C} - \text{N} - \text{Z} \\ | \quad \quad | \\ \text{X} \quad \quad \text{Y} \end{array}$$

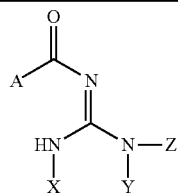
No.	A	X	Y	Z
I-2	4-chlorophenyl		H	4-chlorophenyl
I-3	3-fluorophenyl		H	3,5-dichlorophenyl
I-4	4-fluorophenyl		H	3-chloro-4-fluorophenyl
I-5	3,4-dichlorophenyl		H	3-chloro-5-fluorophenyl
I-6	3,4-difluorophenyl		H	3-trifluoromethylphenyl
I-7	4-trifluoromethylphenyl		H	3-cyclopropylphenyl
I-8	3-chlorophenyl		H	3-tert-butylphenyl
I-9	4-chlorophenyl		H	2-cyclopropylphenyl

-continued



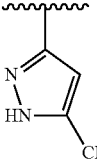
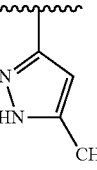
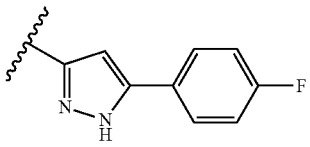
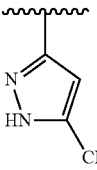
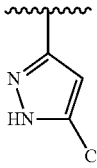
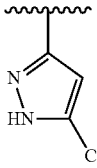
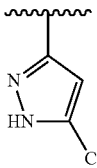
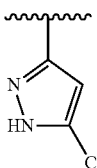
No.	A	X	Y	Z
I-10	3-fluorophenyl		H	2-cyclopropyl-4-fluorophenyl
I-11	4-fluorophenyl		H	3-chlorobenzyl
I-12	3,4-dichlorophenyl		H	4-chlorobenzyl
I-13	3,4-difluorophenyl		H	3-fluorobenzyl
I-14	4-trifluoromethylphenyl		H	4-fluorobenzyl
I-15	3-chlorophenyl		H	3-chloro-5-fluorobenzyl
I-16	4-chlorophenyl		H	3,5-dichlorobenzyl

-continued

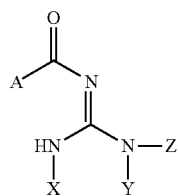


No.	A	X	Y	Z
I-17	3-fluorophenyl		H	3,5-difluorobenzyl
I-18	4-fluorophenyl		H	3-cyclopropylbenzyl
I-19	3,4-dichlorophenyl		H	3-trifluoromethylbenzyl
I-20	3,4-difluorophenyl		H	4-trifluoromethylbenzyl
I-21	4-trifluoromethylphenyl		H	cyclopropyl
I-22	3-chlorophenyl		H	cyclopentyl
I-23	4-chlorophenyl		H	cyclohexyl
I-24	3-fluorophenyl		H	4-methylcyclohexyl

$$\begin{array}{c} \text{O} \\ \parallel \\ \text{A} - \text{C} - \text{N} \\ \parallel \\ \text{HN} - \text{C} - \text{N} - \text{Z} \\ | \quad \quad | \\ \text{X} \quad \quad \text{Y} \end{array}$$

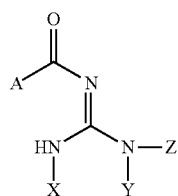
No.	A	X	Y	Z
I-25	4-fluorophenyl		H	ethyl
I-26	3,4-dichlorophenyl		H	tert-butyl
I-27	3,4-difluorophenyl		H	2,2,2-trifluoroethyl
I-28	4-trifluoromethylphenyl		H	1-methylcyclobutyl
I-29	3-chlorophenyl		H	3-chloro-4-fluorophenyl
I-30	4-chlorophenyl		H	3-chloro-5-fluorophenyl
I-31	3-fluorophenyl		H	3-chlorophenyl
I-32	4-fluorophenyl		H	4-chlorophenyl

-continued



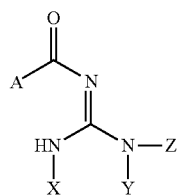
No.	A	X	Y	Z
I-33	3,4-dichlorophenyl		H	3,5-dichlorophenyl
I-34	3,4-difluorophenyl		H	3-chloro-4-fluorophenyl
I-35	4-trifluoromethylphenyl		H	3-chloro-5-fluorophenyl
I-36	3-chlorophenyl		H	3-trifluoromethylphenyl
I-37	4-chlorophenyl		H	3-chlorophenyl
I-38	3-fluorophenyl		H	4-chlorophenyl
I-39	4-fluorophenyl		H	3,5-dichlorophenyl

-continued



No.	A	X	Y	Z
I-40	3-chlorophenyl		—C(O)Me	3-chlorophenyl
I-41	4-chlorophenyl		—C(O)Me	4-chlorophenyl
I-42	3-trifluorophenyl		—C(O)Me	3-chloro-4-fluorophenyl
I-43	3-fluorophenyl		—CH <sub>3</sub>	3-chlorophenyl
I-44	4-fluorophenyl		—CH <sub>3</sub>	4-chlorophenyl
I-45	3-trifluorophenyl		—CH <sub>3</sub>	3-chloro-4-fluorophenyl
I-47			H	3-chloro-4-fluorophenyl

-continued



No.	A	X	Y	Z
I-48			H	4-chlorophenyl
I-49			H	3-chloro-4-fluorophenyl
I-51			H	3-chloro-4-fluorophenyl
I-52			H	4-chlorophenyl
I-53			H	3-chloro-4-fluorophenyl
I-55			H	3-chloro-4-fluorophenyl
I-56	4-trifluoromethylphenyl		H	tert-butyl

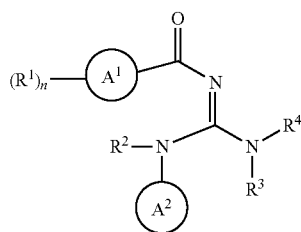
-continued

No.	A	X	Y	Z
I-57			H	tert-butyl
I-58			H	tert-butyl
I-59			H	
I-60			H	tert-butyl.

30. The compound of claim 21, wherein R<sup>3</sup> is phenyl substituted with 1 or 2 substituents independently selected from the group consisting of chloro, fluoro, and trifluoromethyl; and R<sup>4</sup> is trifluoromethyl.

31. A pharmaceutical composition comprising a compound of claim 30 and a pharmaceutically acceptable carrier.

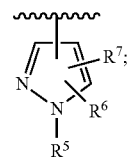
32. A compound represented by Formula I:



including all stereoisomers, geometric isomers, and tautomers; or a pharmaceutically acceptable salt or solvate of any of the foregoing; wherein:

A<sup>1</sup> is phenyl or a six-membered heteroaryl;

A<sup>2</sup> is



R<sup>1</sup> represents independently for each occurrence halogen, haloalkyl, alkyl, cycloalkyl, heterocycloalkyl, hydroxyl, C<sub>1</sub>-C<sub>6</sub>alkoxy, cyano, —CO<sub>2</sub>R<sup>8</sup>, —C(O)R<sup>9</sup>, —S(O)R<sup>9</sup>, —SO<sub>2</sub>R<sup>9</sup>, —SO<sub>2</sub>N(R<sup>10</sup>)(R<sup>11</sup>), —C(O)N(R<sup>10</sup>)(R<sup>11</sup>), —N(R<sup>10</sup>)(R<sup>11</sup>), or —N(R<sup>8</sup>)C(O)(R<sup>9</sup>);



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$R^2$  is hydrogen or alkyl;  
 $R^3$  is aryl, aralkyl, cycloalkyl,  $-(C(R^8)_2)_m$ -cycloalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl,  $-(C(R^8)_2)_m$ -heterocycloalkyl, alkyl, haloalkyl, hydroxyalkyl,  $-(C(R^8)_2)_m$ -alkoxy,  $-(C(R^8)_2)_m$ -O $-(C(R^8)_2)_m$ -alkoxy, or  $-(C(R^8)_2)_m$ -CN, wherein said aryl, aralkyl, cycloalkyl, heteroaryl, heteroaralkyl, and heterocycloalkyl are each optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, haloalkyl, hydroxyl, alkyl, cycloalkyl, hydroxyalkyl,  $C_1$ - $C_6$ alkoxy, cyano, and  $-C_1$ - $C_6$ alkylene- $CO_2R^8$ ;  
 $R^4$  is hydrogen, alkyl, or  $-C(O)R^9$ ; or  $R^3$  and  $R^4$  are taken together with the nitrogen atom to which they are attached to form a 3 to 7 membered heterocyclic ring optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, haloalkyl, hydroxyl, alkyl, cycloalkyl, and  $C_1$ - $C_6$ alkoxy;  
 $R^5$  is hydrogen or alkyl;  
 $R^6$  is alkyl, cycloalkyl, haloalkyl, cyano, aryl, aralkyl, heteroaryl, heteroaralkyl,  $-CO_2R^8$ , or  $-C(O)N(R^{10})(R^{11})$ , wherein said cycloalkyl, aryl, aralkyl, heteroaryl,

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and heteroaralkyl are each optionally substituted with 1 or 2 substituents independently selected from the group consisting of halogen, haloalkyl, hydroxyl, alkyl, hydroxyalkyl,  $C_1$ - $C_6$ alkoxy,  $-O$ -aralkyl, and cyano;  
 $R^7$  is hydrogen, halogen, alkyl, or haloalkyl;  
 $R^8$  represents independently for each occurrence hydrogen, alkyl, or cycloalkyl; or two occurrences of  $R^8$  attached to the same carbon atom are taken together with said carbon atom to form a saturated carbocyclic ring;  
 $R^9$  represents independently for each occurrence alkyl or cycloalkyl;  
 $R^{10}$  and  $R^{11}$  each represent independently for each occurrence hydrogen, alkyl, or cycloalkyl; or  $R^{10}$  and  $R^{11}$  are taken together with the nitrogen atom to which they are attached to form a 3 to 7 membered heterocyclic ring optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, haloalkyl, hydroxyl, alkyl, cycloalkyl, and  $C_1$ - $C_6$ alkoxy;  
 $n$  is 0; and  
 $m$  is 1, 2, 3, 4, or 5.

\* \* \* \* \*